An enantioselective synthesis of substituted 1,2,3,4,5,6-hexahydro-2,6-methano-3-benzazocines

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An Enantioselective Synthesis of Substituted 1,2,3,4,5,6-Hexahydro-2,6-Methano-3-Benzazocines

Submitted by Colin Stephen Williams

for the degree of PhD

of the University of Bath

1990

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To my parents

"There is a theory which states that if ever anyone discovers exactly what the Universe is for and why it is here, it will instantly disappear and be replaced with something even more bizarre and inexplicable."

"There is another theory which states that this has already happened."

Douglas Adams, 1980

Acknowledgements

I would like to express my thanks to my supervisor, Dr. Malcolm Sainsbury, for his support and advice during the period of my research work at Bath and for his patience during the year it has taken me to write this thesis. I would also like to take this opportunity to thank his colleagues within the organic chemistry department and all the technical and general staff in the School of Chemistry for their time and assistance. I also express my thanks my industrial supervisor, Dr. Alan Naylor, and Glaxo Group Research Ltd., Ware, as a whole, where I spent three months as a part of my CASE award with Glaxo.

SUMMARY

The work outlined in this thesis was conducted between October 1986 and November 1989 and is primarily concerned with the chiral and stereoselective synthesis of substituted 1,2,3,4,5,6-hexahydro-2,6-methano-3-benzazocine derivatives.

(-)-(1*R*,2*S*,4*R*,6*R*)-1,2,3,4,5,6-Hexahydro-8-methoxy-1,3,4,6-tetramethyl-2,6-methano-3-benzazocine was synthesised in 86% enantiomeric excess from the *trans*-η^6-chromium tricarbonyl complex of (+)-(2*R*,1'*S*)-1-(1,2-dihydro-7-methoxy-1,4-dimethyl-1-naphthyl)-*N*-methyltrifluoroacetyl-2-propylamine by treatment with ultrasound in a methanolic solution of potassium carbonate. Chirality was introduced into the synthetic route using an Enders' type *C*-alkylation of the (*S*)-1-amino-2-methoxymethylpyrrolidine hydrazone of 4-(3-methoxyphenyl)-4-methylcyclohexanone. A Beckmann rearrangement of the chiral cyclohexanone, followed by ring opening of the resulting caprolactam gave an aminooctanone derivative, which was converted to (+)-(2*R*,1'*S*)-1-(1,2-dihydro-7-methoxy-1,4-dimethyl-1-naphthyl)-*N*-methyltrifluoroacetyl-2-propylamine *via* a cyclo-dehydration reaction.

CONTENTS

INTRODUCTION

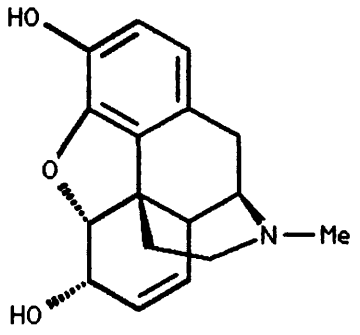
INTRODUCTION

1.1 Biological and Pharmacological Background to the Project

The latex obtained by incision of the unripe seed capsule of the poppy, *Papaver somniferum*, and known as opium, is the source of several important alkaloids. The use of poppy juice to induce a sense of euphoria and sedation was first recorded by Theophrastus in the third century B.C.

In 1803 the German pharmacist, Seturner, isolated morphine (1) as one of the active ingredients of opium (which he named after Ovid's god of dreams), but its structure was not elucidated until 120 years later by Gulland and Robinson[1] and later by Schöpf.[2]

Figure 1



(1)

Morphine is of great clinical value, because of its ability to relieve severe pain without rendering the subject unconscious. However, in addition morphine also induces drowsiness; alters mood, often causing euphoria and physical dependence; reduces gut/intestinal tract motility; causes nausea and vomiting, and exerts a direct action on the respiratory centre by reducing its responsiveness to carbon dioxide tension. The latter effect can lead to respiratory collapse and death in the case of overdose. Regular use of morphine can lead to morphine tolerance in the subject, requiring

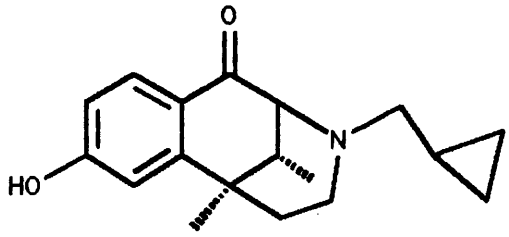
greater and greater doses to give the same effect.

A need to produce analgesic drugs which do not possess the adverse effects described above, has prompted much research in the field of opioid chemistry.

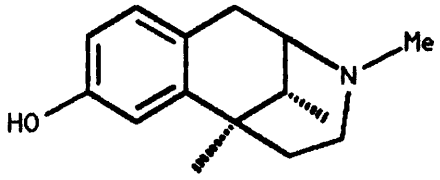
Morphine and related compounds act upon pain receptors in the central nervous system to produce an analgesic effect. However, the precise nature of these receptors is not known. In 1976 Martin *et al.*[3] described three different syndromes, produced by the congeners of morphine in the non-dependent chronic spinal dog, that were attributed to three distinguishable receptors. (The existence of more than one receptor type had been predicted for some years before on the basis that certain hexahydro-2,6-methano-3-benzazocines have a different biological effect to that of morphine.)

Three receptors types were suggested: μ- (morphine is the typical agonist), κ- (agonised by ketocyclazocine, 2) and σ- (agonised by the *N*-allyl analogue of α-metazocine, 3). It was not until after the

Figure 2



(2)



(3)

isolation of the endorphins and enkephalins (analgesic peptides related to the body's natural pain killing compounds) that a fourth receptor site called the δ-receptor (found to be plentiful in mouse vas deferens tissue) was proposed.[4]

Of these receptors, the μ-receptor site is linked with analgesia and the σ-receptor site is linked with psychotomimetic effects,

whereas the effects of the κ- and δ-receptor sites remains unclear. Most opioid drugs act at more than one receptor and to varying degrees. This complicates the interpretation of events further.

Hexahydro-2,6-methano-3-benzazocines are of interest, because most studies report both analgesic agonist and antagonist responses in a variety of tests, with "side effects" such as dependence and respiratory depression being greatly reduced. These compounds are thought to differ from morphine in that they are agonists of the κ-receptor. The topic of pain receptor sites is too large and complex to be fully discussed here, but various in depth discussions exist elsewhere in the literature.[5]

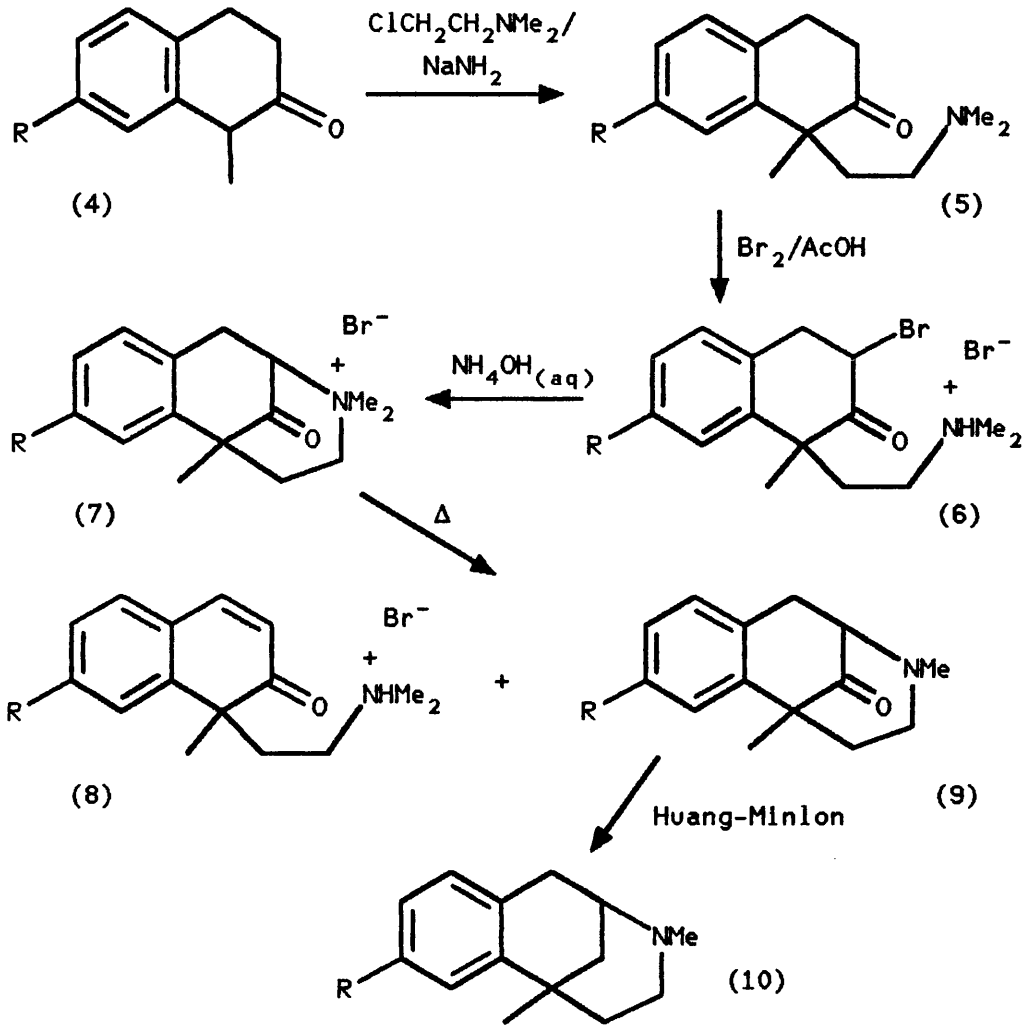
1.2 Syntheses of Substituted Hexahydro-2,6-methano-3-benzazocines

There are two principal approaches to substituted hexahydro-2,6-methano-3-benzazocines. These are the tetralone route, originally performed by Barltrop[6] and later adapted by May *et al.*,[7] and the Grewe cyclisation[8] of tetrahydropyridines. A short summary of the main variants of these two routes follows. Routes involving dihydronaphthalenes as the precursor to the target compounds, as well as existing chiral syntheses are also detailed below.

1.2.1 The Tetralone Route

The synthesis of 3,6-dimethyl-1,2,3,4,5,6-hexahydro-2,6-methano-3-benzazocine by May *et al.*[7] (see Scheme 1) involves initial alkylation at C-1 of a 1-alkyl-2-tetralone (4) with 2-chloro-*N*,*N*-dimethylethanamine, followed by bromination at C-3 and subsequent ring closure with aqueous ammonia. Heating leads to *N*-demethylation of the quaternary ammonium salt (7) to the tertiary amine (9). Reduction of the ketone function, using the Huang-Minlon

Scheme 1

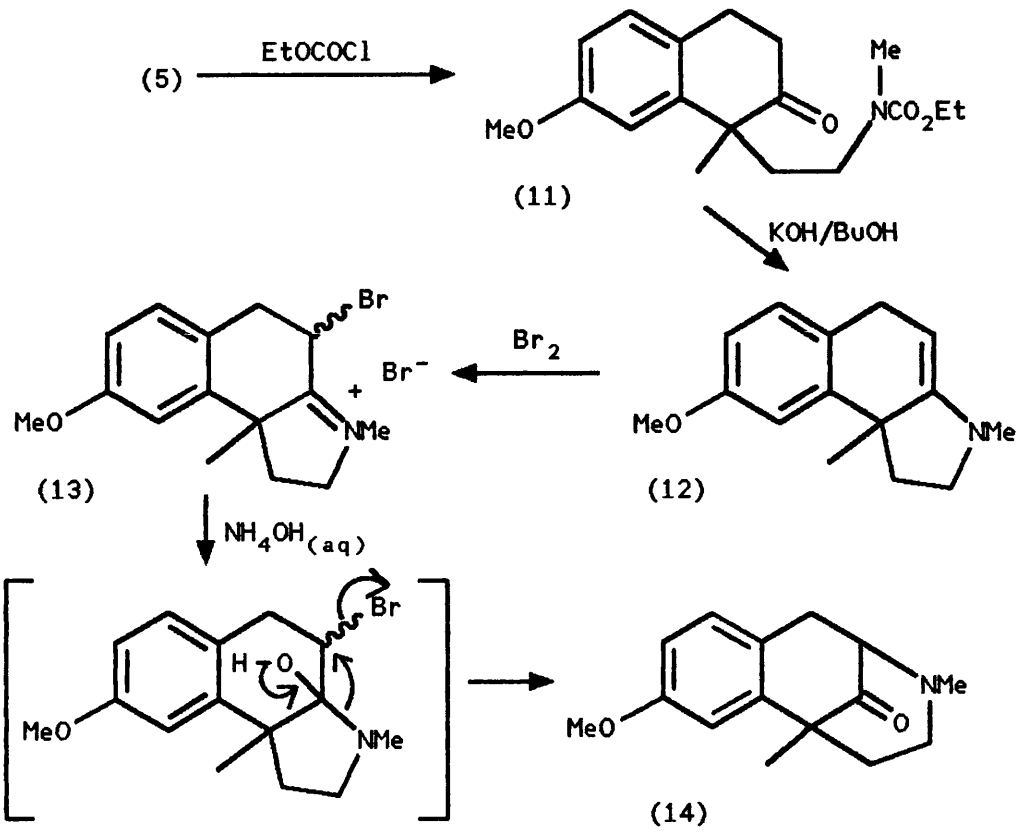


method, gives the required hexahydro-2,6-methano-3-benzazocine (10).

Low yields in the C-1 alkylation of the 2-tetralone (4) and the *N*-demethylation of the quaternary salt (7) (see Scheme 1) led to the alternative strategies of Takeda and others[9] and of May and Murphy[10] shown in Scheme 2 and Scheme 3 respectively.

The route shown in Scheme 2 involves treating the alkylated 2-tetralone (5) with ethyl chloroformate to give the ethyl carbamate (11), which on hydrolysis of the carbamate group forms an enamine (12). Bromination of the enamine (12), followed by hydrolysis and rearrangement of the resultant iminium salt (13) gives the 11-oxo-hexahydro-2,6-methano-3-benzazocine (14).

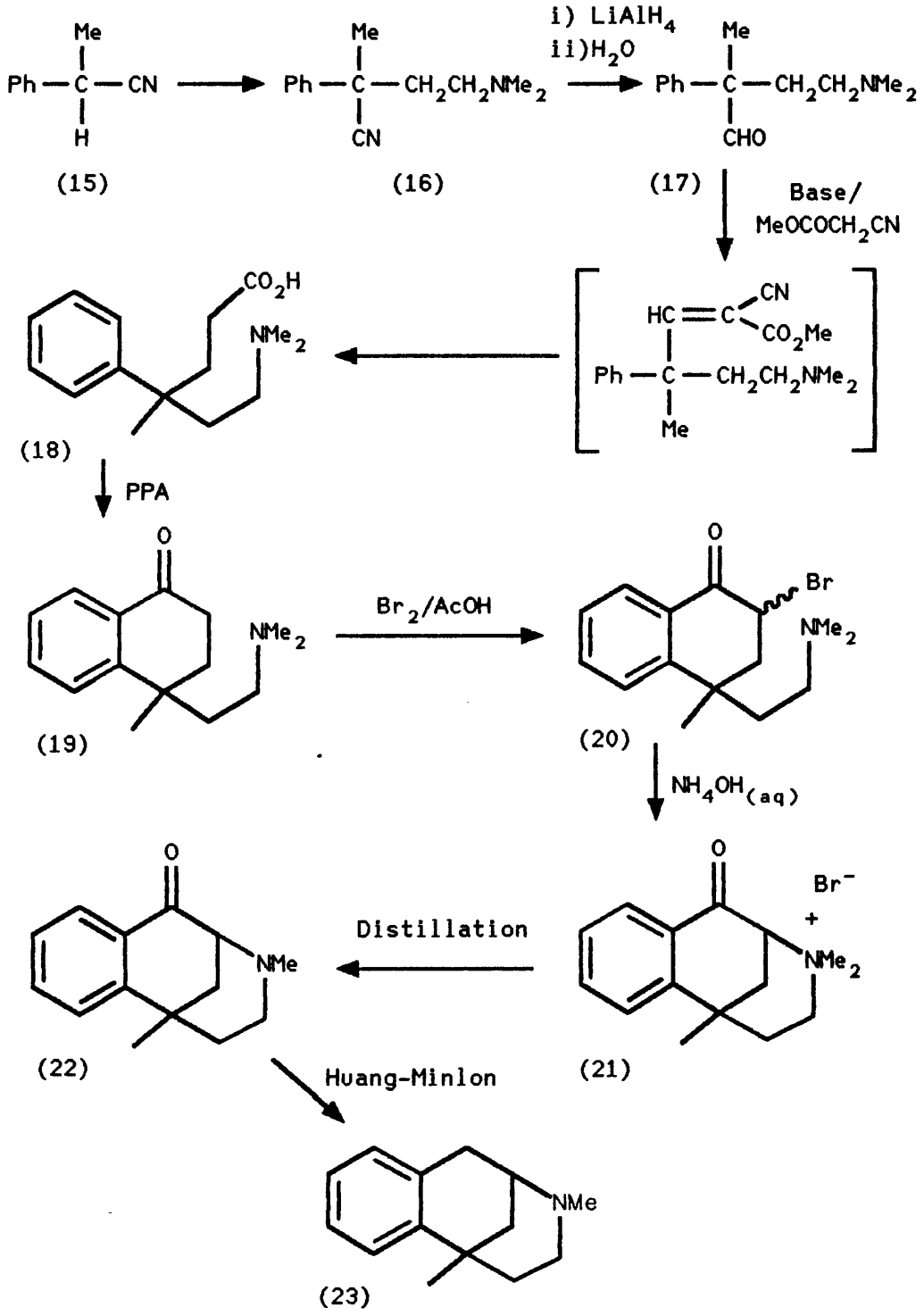
Scheme 2



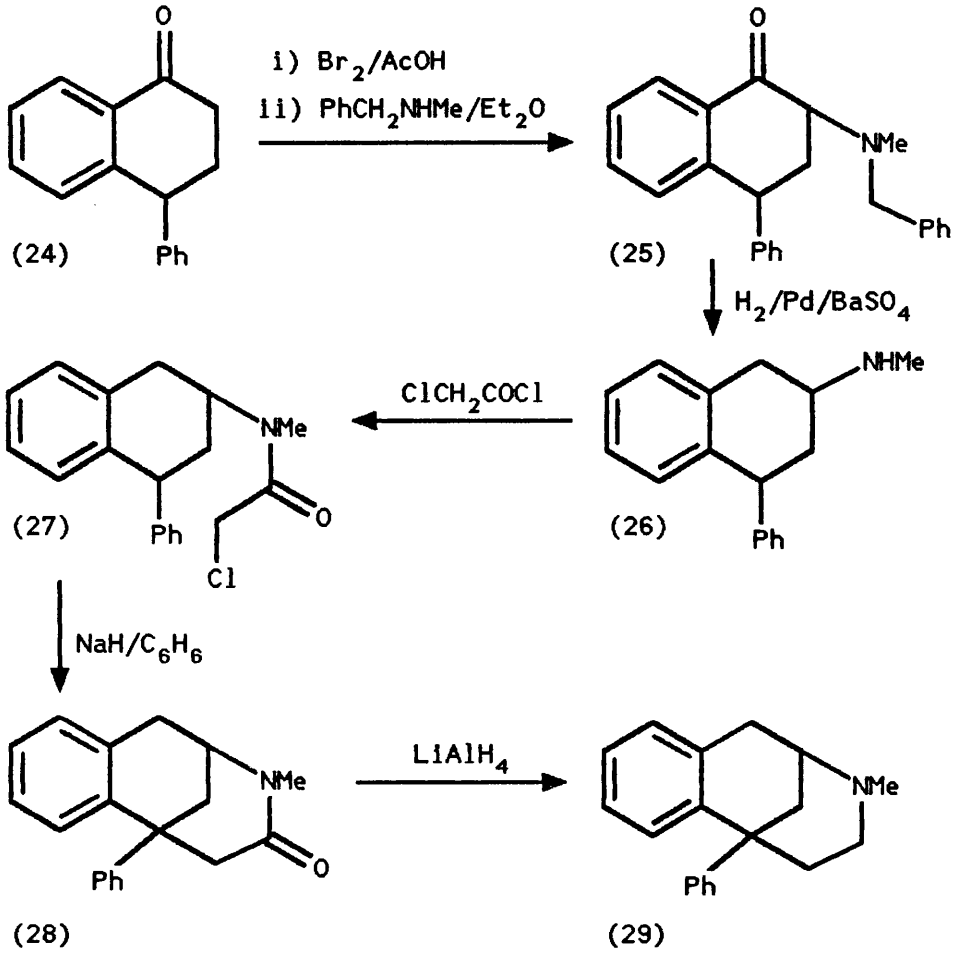
The route of May and Murphy[10] uses a 1-tetralone derivative (19) as an intermediate. This 1-tetralone (19) is synthesised from 2-phenylpropanonitrile (15), which is treated with base and then alkylated with 2-chloro-*N*,*N*-dimethylethanamine. Several steps then lead to the formation of the acid (18), which is converted to the 1-tetralone (19) by a cyclodehydration reaction using polyphosphoric acid (PPA). From the 1-tetralone (19) onwards the route closely resembles the one of May *et al.*[7] shown in Scheme 1.

4-Phenyl-1-tetralone (24) has also been used as a starting material in the synthesis of 6-phenyl-1,2,3,4,5,6-hexahydro-2,6-methano-3-benzazocine.[11] (See Scheme 4.) 4-Phenyl-1-tetralone (24) is first brominated and then the bromide undergoes a nucleophilic substitution reaction with benzylmethylamine to give the benzyl

Scheme 3


i) LiAlH4
ii)H2O
(15)
(16)
(17)
Base/
MeOCOCH2CN
(18)
PPA
(19)
Br2/AcOH
(20)
NH4OH(aq)
(21)
Distillation
(22)
Huang-Minlon
(23)

Scheme 4

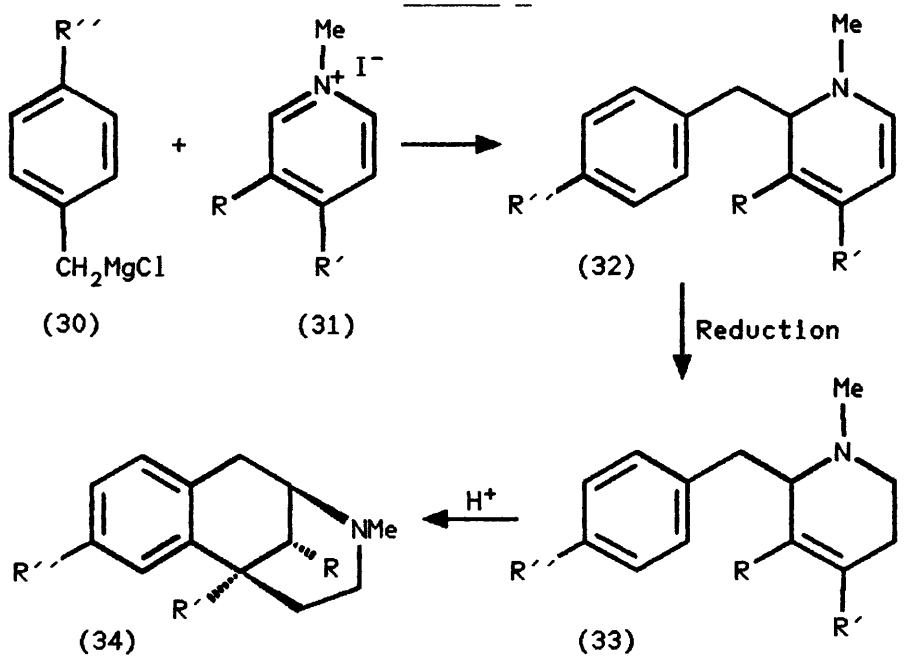


protected amine (25). Hydrogenation over a catalyst of palladium on barium sulphate reduced the carbonyl and benzyl functionalities. Treatment with chloroacetyl chloride gave the chloroacetamide (27), which underwent ring closure in the presence of sodium hydride. Reduction with lithium aluminium hydride gave the required 3-methyl-6-phenyl-1,2,3,4,5,6-hexahydro-2,6-methano-3-benzazocine (29).

1.2.2 The Grewe Cyclisation

In an analogous route to a synthesis of morphinans from 1,2,3,4,5,6,7,8-octahydroisoquinolines by Grewe,[8] May and Fry[12] prepared substituted hexahydro-2,6-methano-3-benzazocines (see Scheme 5). Reaction of 3,4-dialkyl or 4-alkylpyridinium methiodides

Scheme 5

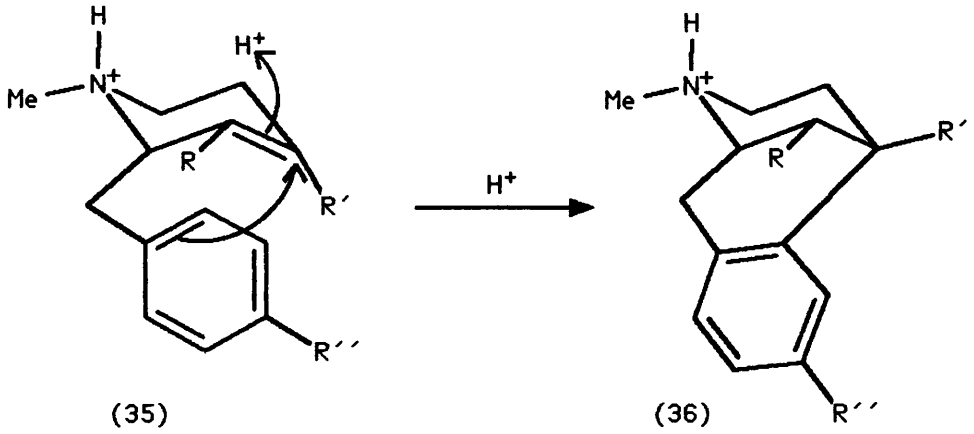


with either benzyl or *p*-methoxybenzyl magnesium chloride, in ether, readily gives dihydropyridines of the required structure (32). Dihydropyridines of this type rapidly decompose, presumably by an auto-oxidative mechanism, unless trapped as stable perchlorate salts.[13] Reduction of the dihydropyridine (32) to the tetrahydropyridine (33) is accomplished using sodium borohydride. Ring closure to give the hexahydro-2,6-methano-3-benzazocine (34) is brought about by treatment with polyphosphoric acid or hydrobromic acid.

In the case of 3,4-dialkyl and 3-alkyltetrahydropyridines the predominant product is the *cis*- or α-compound (see Scheme 6). However, it is the *trans*- or β-compound that is observed to be the greater analgesic in rodent studies.

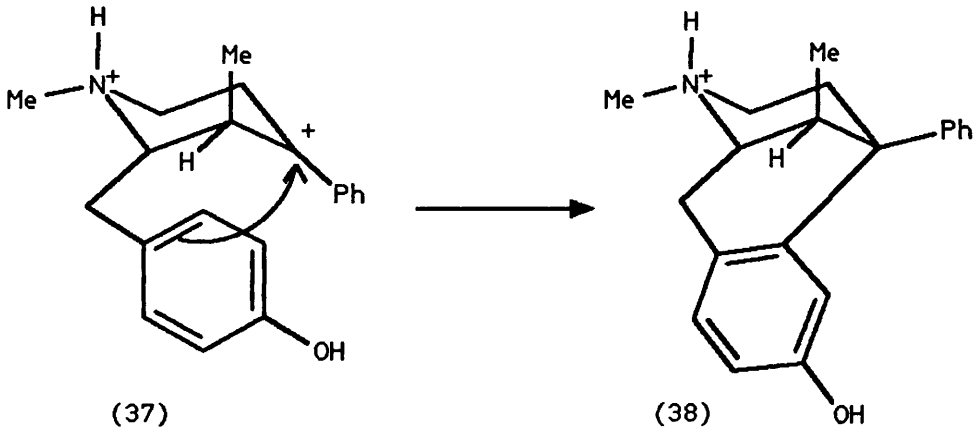
For (36, R = Me, R' = Me), only 1% of the *trans*- or β-isomer was isolated. In contrast 3-alkyl-4-phenyltetrahydropyridines (37) give mainly the *trans*- or β-isomer (see Scheme 7). Yokoyama *et al.*[14] suggested that in this case the 4-phenyl group stabilizes the largely *trans*-benzyl carbonium ion intermediate. (The *trans*-benzyl

Scheme 6



(35) (36)

Scheme 7

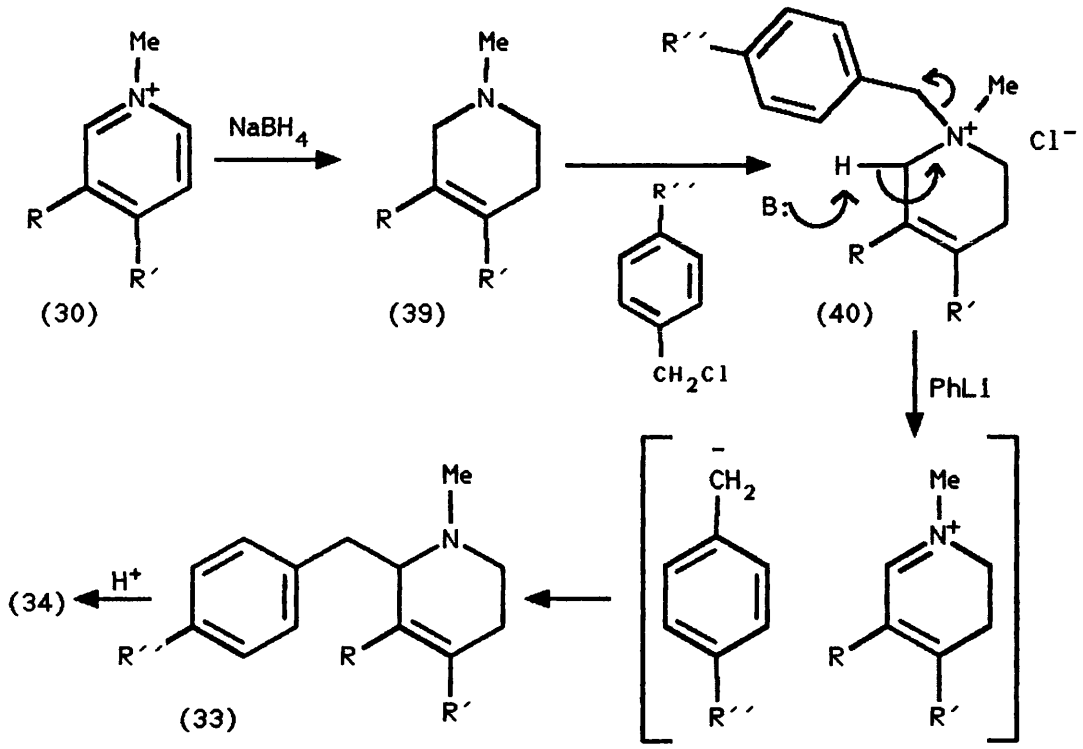


(37) (38)

intermediate is less sterically hindered than the *cis*-benzyl intermediate.)

An alternative approach to the formation of the 2-benzyl-tetrahydropyridine (33) employs a phenyl lithium induced Stevens' rearrangement introduced by Fry and May.[15] On adding phenyl lithium to the benzyl tetrahydropyridine salt (40) rearrangement occurs to give mainly the required 2-substituted product. (See Scheme 8.)

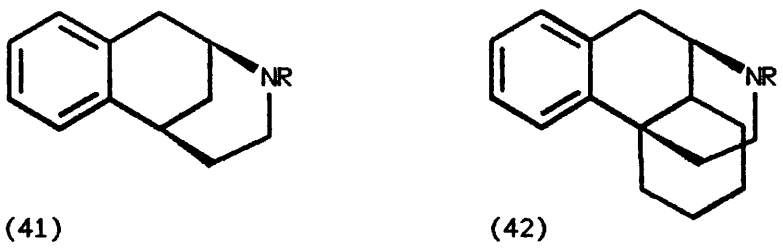
Scheme 8



1.2.3 Syntheses Using Dihydronaphthalene Intermediates

Several syntheses of hexahydro-2,6-methano-3-benzazocines (41) and morphinans (42) exist that use dihydronaphthalenes as key

Figure 3

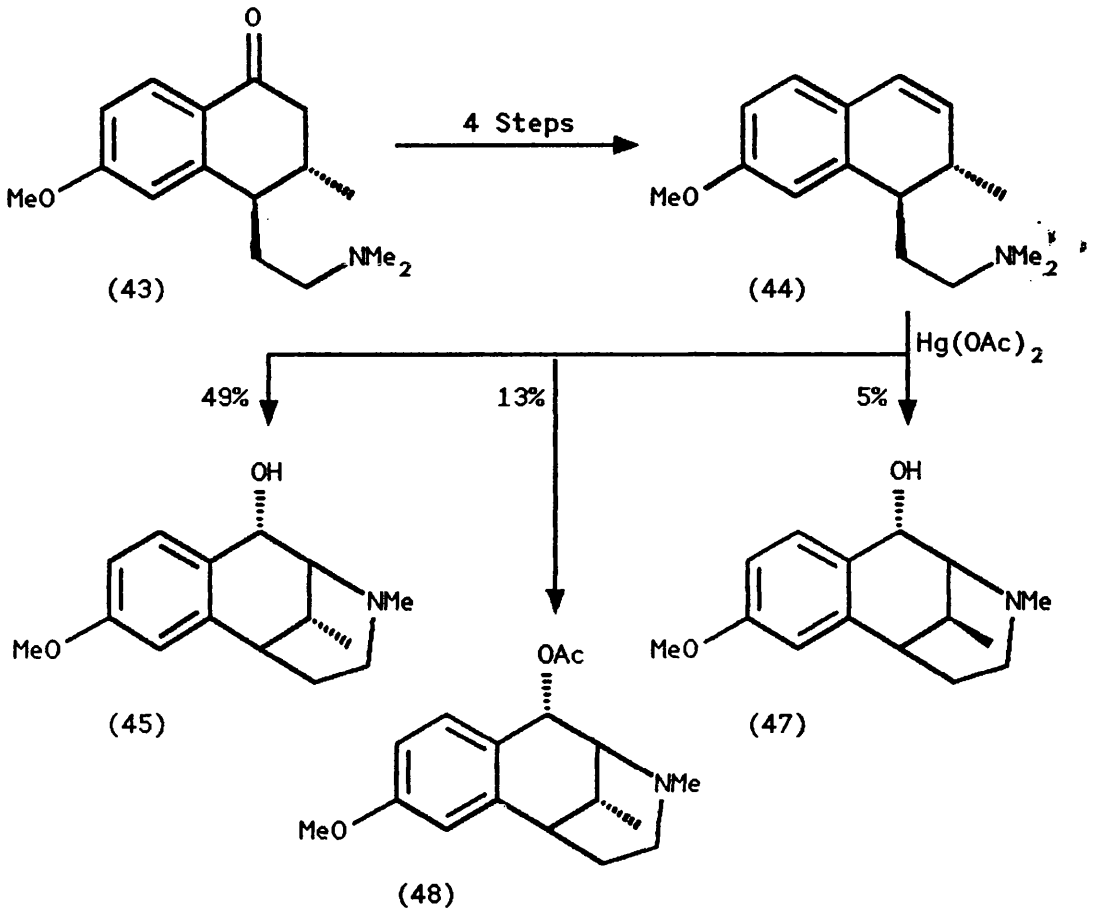


(41) (42)

intermediates in the formation of the final ring.

May and Inoue[16] first synthesised the 1,2-dihydronaphthalene (44), in four steps, from a 1-tetralone (43) intermediate. Treatment with mercuric acetate led to ring closure by means of attack of the mercury(II) - double bond complex by the amino group. As can be seen from Scheme 9, this reaction gives a reasonable level of

Scheme 9

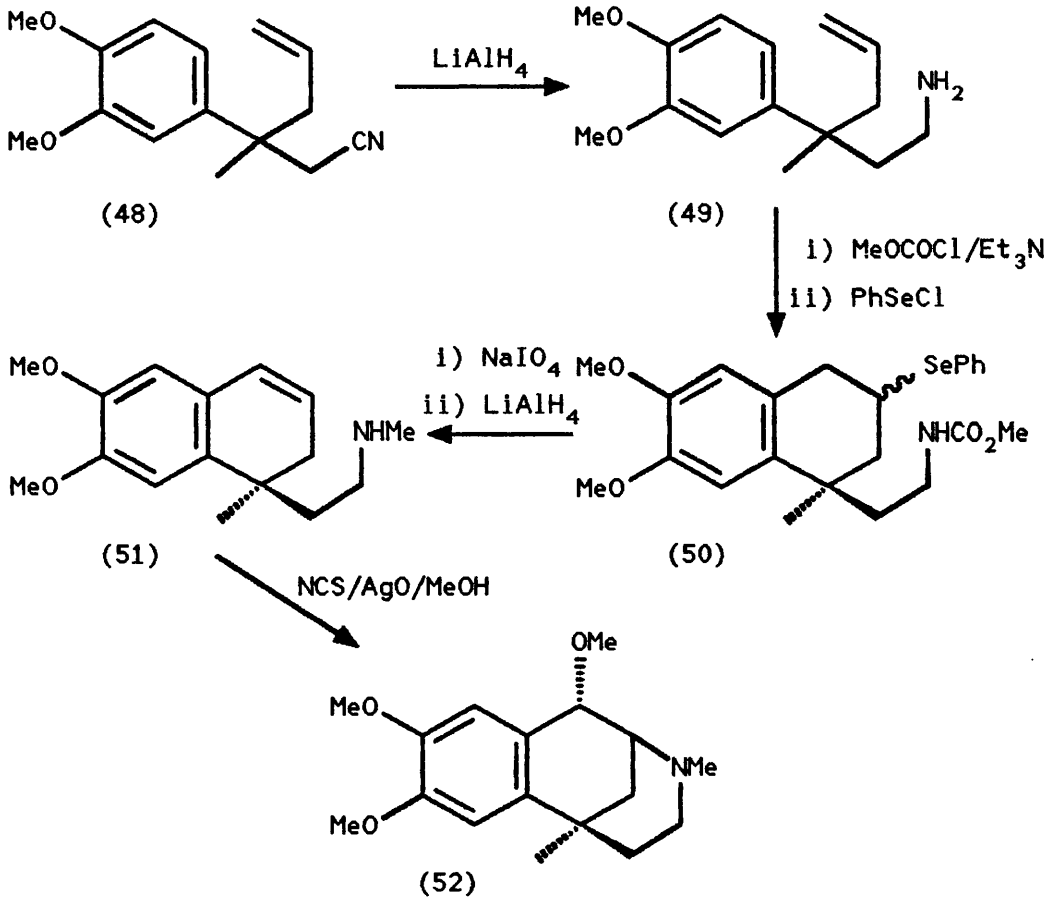


stereo-control in the hydroxylation at C-1, but leads to some epimerization at C-11.

In recent years other syntheses using dihydronaphthalenes have been developed. Kametani *et al.*[17] have designed a synthesis employing *N*-chlorosuccinimide (NCS) to form a *N*-chloroamine. Decomposition of this *N*-chloroamine on silver oxide in the presence of methanol gives the 1-methoxy-1,2,3,4,5,6-hexahydro-2,6-methano-3-benzazocine (52) in a stereoselective manner (see Scheme 10). In a related synthesis of a morphinan (53) Kametani *et al.*[18] decomposed the *N*-chloroamine on titanium(III) chloride in the presence of dichloromethane to give the chloro derivative instead of the methoxy compound.

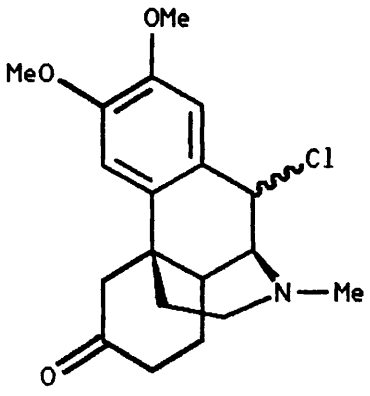
Another morphinan synthesis of Tius and Therkauf[19] made use

Scheme 10



(52)

Figure 4

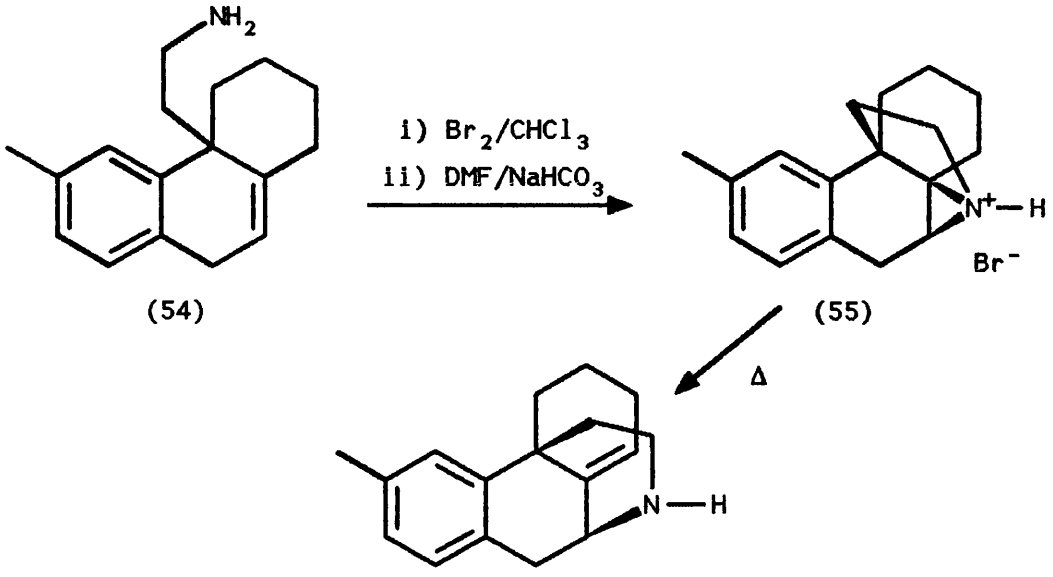


(53)

of aziridinium salt as an intermediate. This aziridinium salt (55) was formed by treating the 1,2-dihydronaphthalene (54) with bromine and then treating the dibromo compound formed with base. On heating the aziridinium salt (55) to 100°C, rearrangement took place to give the

required morphinan (56). (See Scheme 11.)

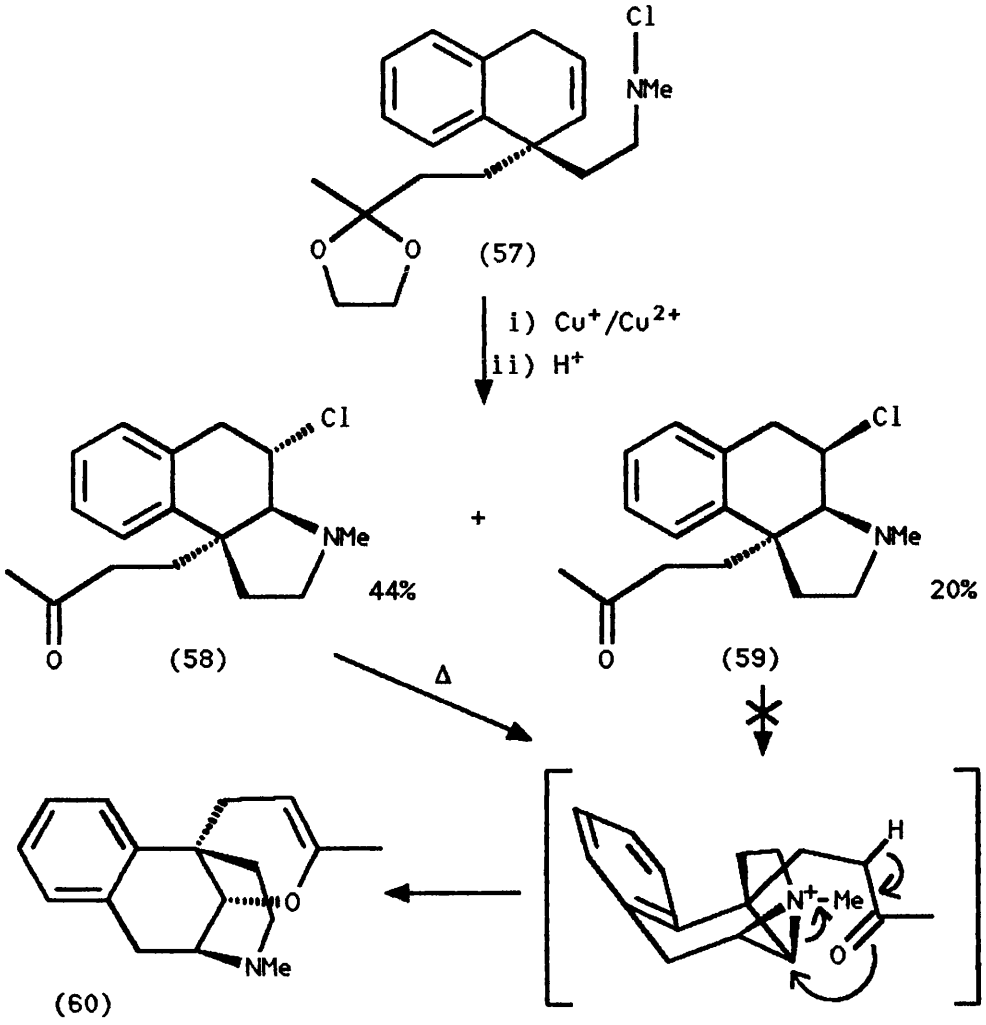
Scheme 11



(54) (55) (56)

The synthesis of Broka and Gerlits[20] combines both the use of a *N*-chloroamine derivative and an aziridinium intermediate. (See Scheme 12.) This time copper(I) and copper(II) are used to catalyse the addition of the *N*-chloroamine to the double bond to give the pyrrolidines, (58) and (59). Only the pyrrolidine (58), where the chlorine atom is in a *trans*-configuration with respect to the nitrogen atom, undergoes rearrangement on heating to give the morphinan (60).

Scheme 12

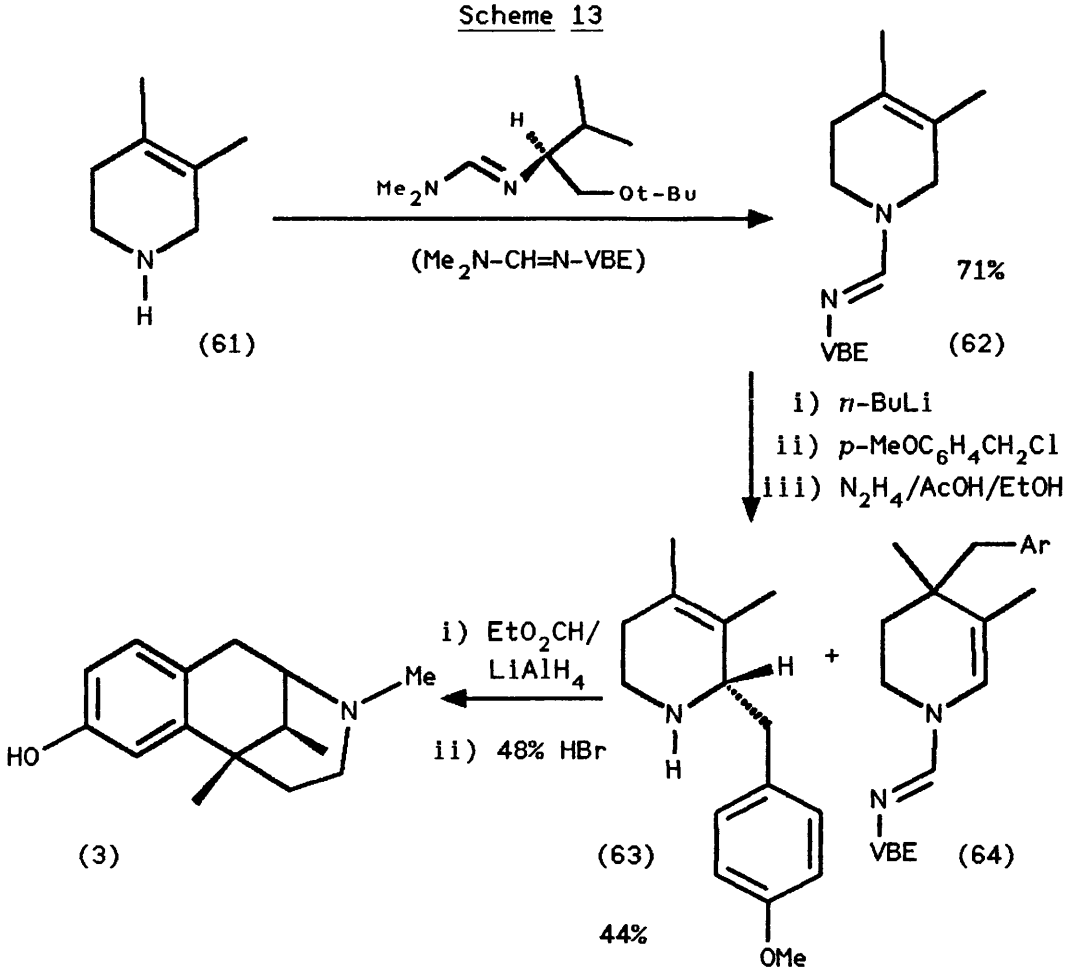


1.2.4 Chiral Syntheses of Hexahydro-2,6-methano-3-benzazocines

At the time of writing there are only three notable chiral syntheses of hexahydro-2,6-methano-3-benzazocines in the literature and two of these are based on the chiral synthesis of tetrahydropyridines from which the final product is obtained by means of a Grewe cyclisation (see Chapter 1.2.2).

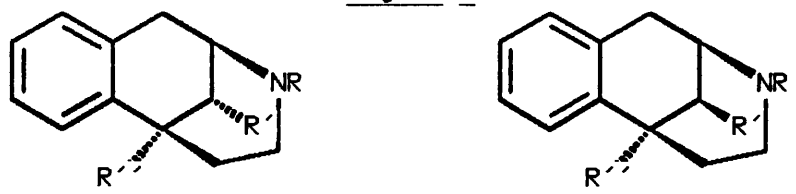
Meyers *et al.*[21] use a chiral formamadine auxiliary, which is attached to the nitrogen of the tetrahydropyridine (62), to perform a chiral alkylation using *p*-methoxybenzyl chloride as the alkylating agent. (See Scheme 13.) An enantiomeric excess of 98% was reported for the synthesis of α-metazocine (3) using this method. However,

Scheme 13



because this synthesis relies on a Grewe cyclisation as its final step, the major product will always be the α-product, which, as stated previously, tend to be less biologically active than the β-form. (See Figure 5.)

Figure 5

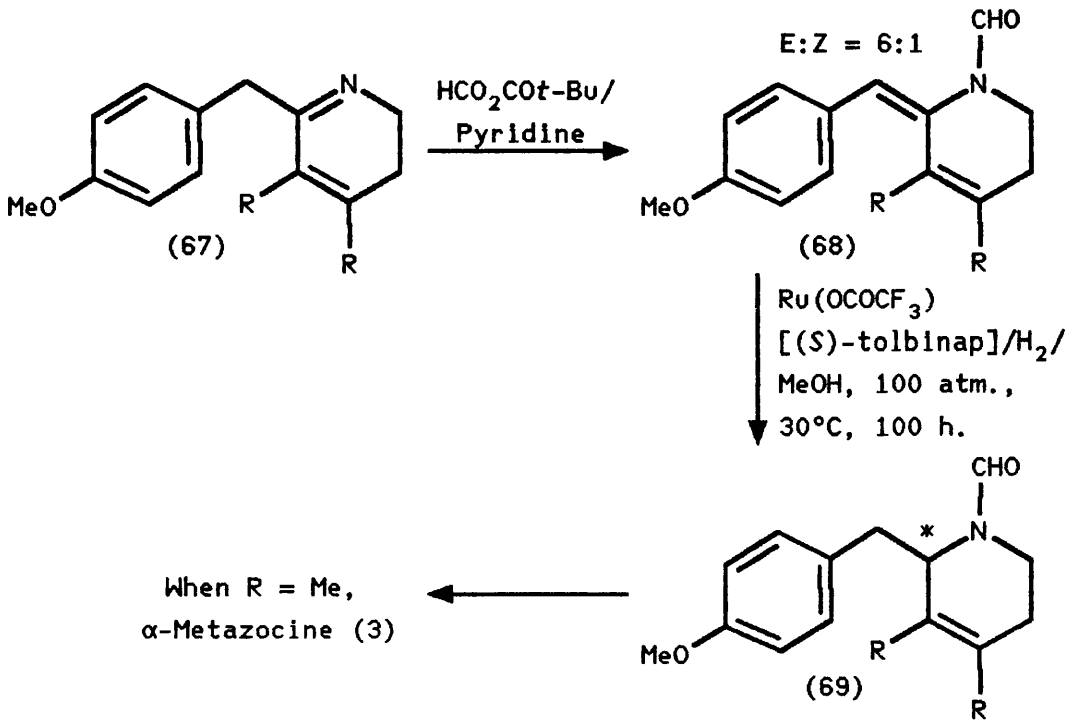


(65) α (66) β

Noyori *et al.*[22] devised a similar type of chiral synthesis, this time relying on the chiral hydrogenation of the enamide (68) using a chiral ruthenium-binap catalyst. This route gave an enantiomeric excess of 97%. (See Scheme 14.) Again only the α-compound is

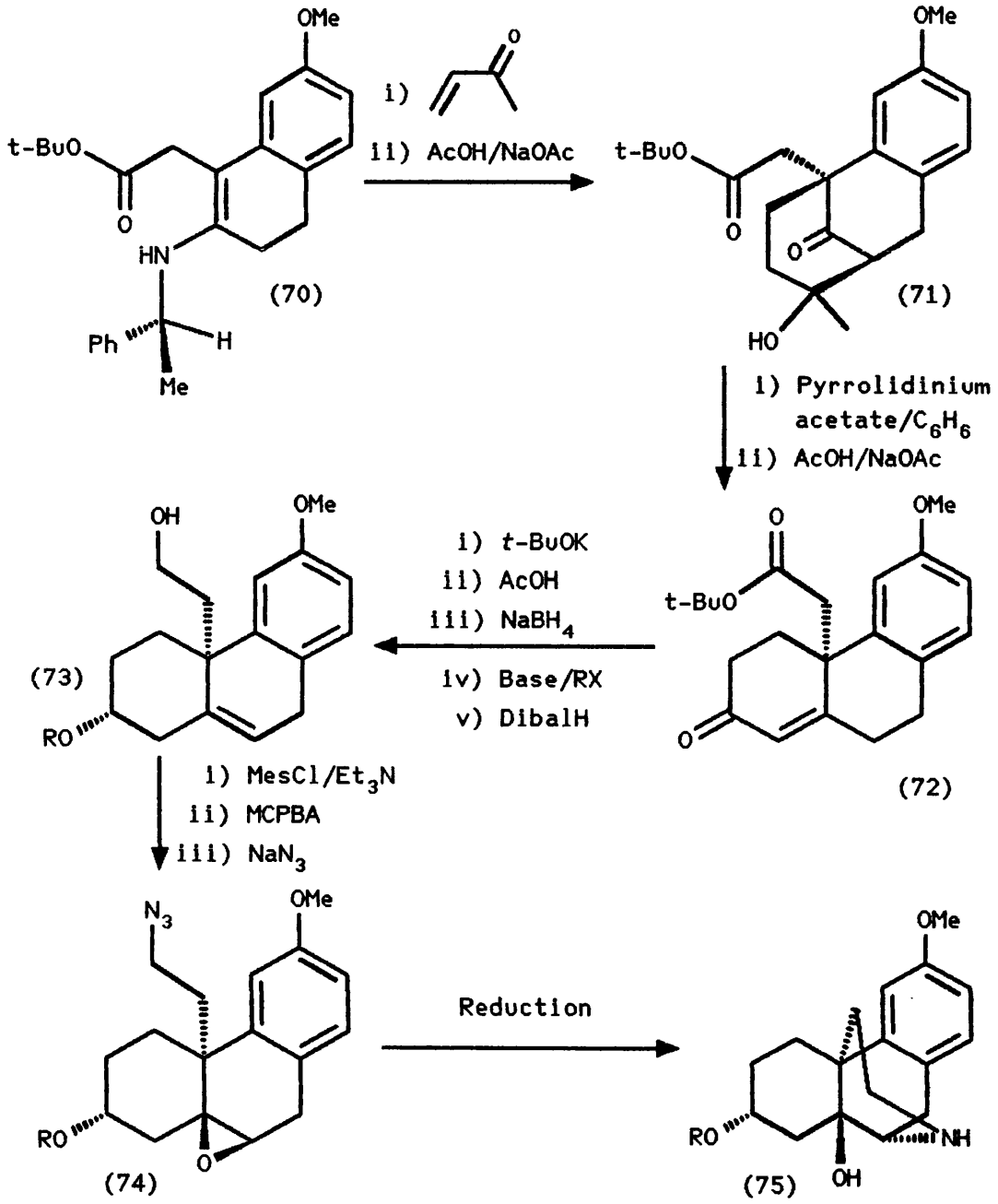
obtainable using this route.

Scheme 14



Recently a chiral synthesis of a morphinan (75) was published by d'Angelo *et al.*,[23] which uses a chiral enamine (see Scheme 15) to induce asymmetry into the molecule. The final ring closure is performed using a route similar to those discussed in Chapter 1.2.3 with a dihydronaphthalene intermediate. In this case the double bond is converted to an epoxide (74), which is attacked by the amino group to give the final ring closed product (75).

Scheme 15


OMe
t-BuO
O
HN
Ph
H
Me
(70)
i)
ii) AcOH/NaOAc
(71)
HO
i) Pyrrolidinium acetate/C_6H_6
ii) AcOH/NaOAc
(72)
i) t-BuOK
ii) AcOH
iii) $NaBH_4$
iv) Base/RX
v) DibalH
(73)
RO
OH
i) $MesCl/Et_3N$
ii) MCPBA
iii) NaN_3
N_3
(74)
Reduction
(75)
NH
OH

RESULTS AND DISCUSSION

RESULTS AND DISCUSSION

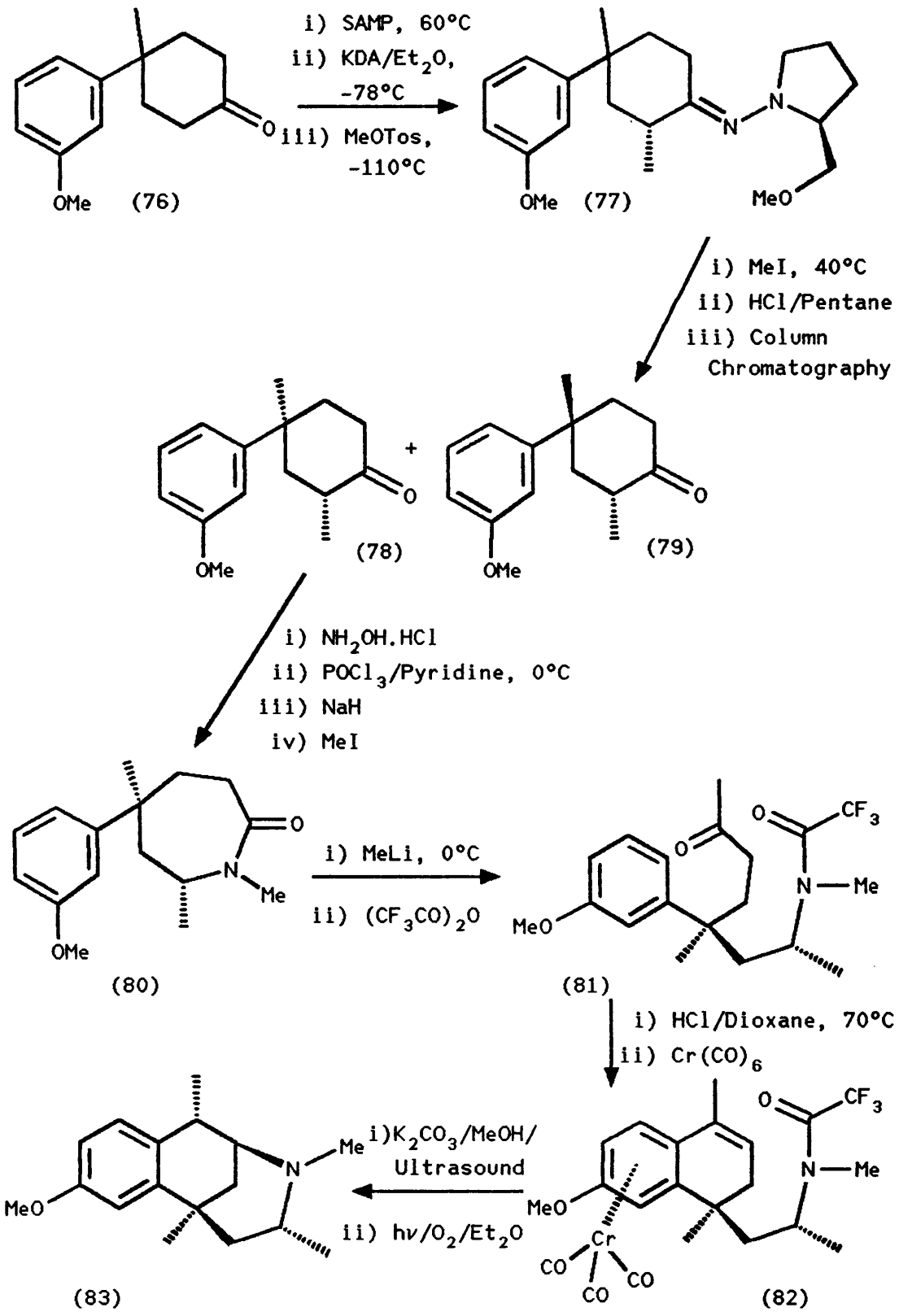
2.1 Basis of the Project

The structure-activity relationships of the different opioid receptors (see Chapter 1.1) are not fully understood, motivating further investigation of novel compounds to increase knowledge of the receptor sites. This has the ultimate goal of producing a non-addictive pain killing drug.

There are relatively few chiral syntheses of 1,2,3,4,5,6-hexahydro-2,6-methano-3-benzazocines in the literature (see Chapter 1.2.4), most relying on chiral resolution as a final step. It was our aim to construct a flexible route to these compounds, which is both stereo- and enantioselective.

A 1,3,4,6,8-substitution pattern was chosen for our target molecule, since this substitution pattern[24] has received little attention, and compounds substituted at C-4[25] are rare. The route selected (see Scheme 16) relies on the introduction of chirality *via* alkylation of a 4,4-disubstituted cyclohexanone (76). Enders' chiral hydrazone method[26] was selected for this purpose. After separation of the resulting two diastereomers by column chromatography, the dimethylcyclohexanone (78) was converted into the oxime (102) and then subjected to a Beckmann rearrangement to give the caprolactam (109). *N*-Methylation, followed by treatment with methyl lithium and trifluoroacetic anhydride quench afforded the ring opened trifluoroacetamidoketone (81). Cyclodehydration yielded the dihydronaphthalene (120), which was treated with chromium hexacarbonyl to selectively give the chromium complex (82). Sonication of the chromium complex (82) with potassium carbonate in aqueous methanol led slowly to the

Scheme 16



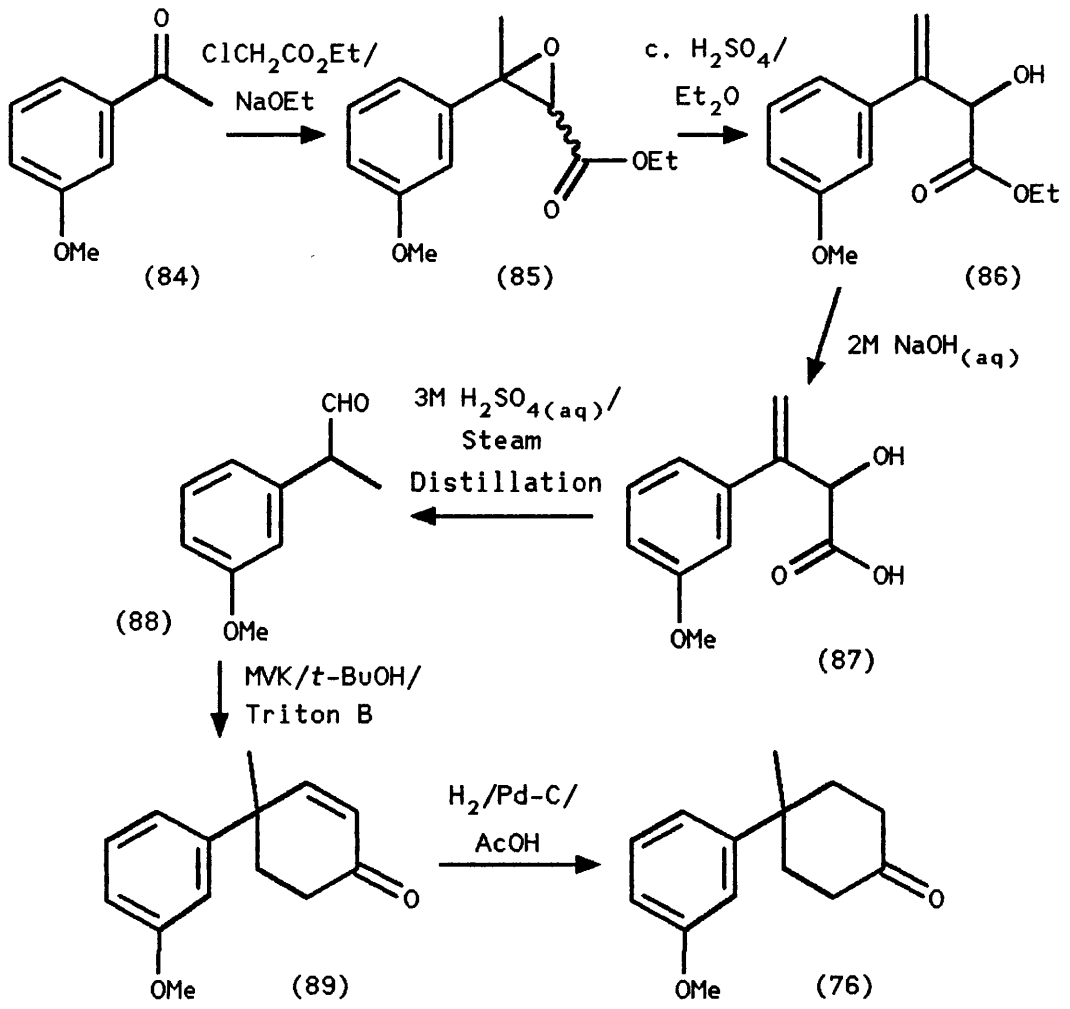
formation of a ring closed product, which was decomplexed to give the hexahydro-2,6-methano-3-benzazocine (83).

2.2 Synthetic Work Towards the Production of Chiral 1,3,4,6,8-Penta-Substituted Hexahydro-2,6-Methano-3-Benzazocines

2.2.1 The Large Scale Synthesis of the Cyclohexanone (76)

The literature route to 4,4-disubstituted cyclohexanones[27] (see Scheme 17) involves first the formation of the aldehyde (88) and then a Robinson annulation using methyl vinyl ketone (MVK) to give the cyclohexenone (89). Hydrogenation of the cyclohexenone (89) gives the required cyclohexanone (76).

Scheme 17

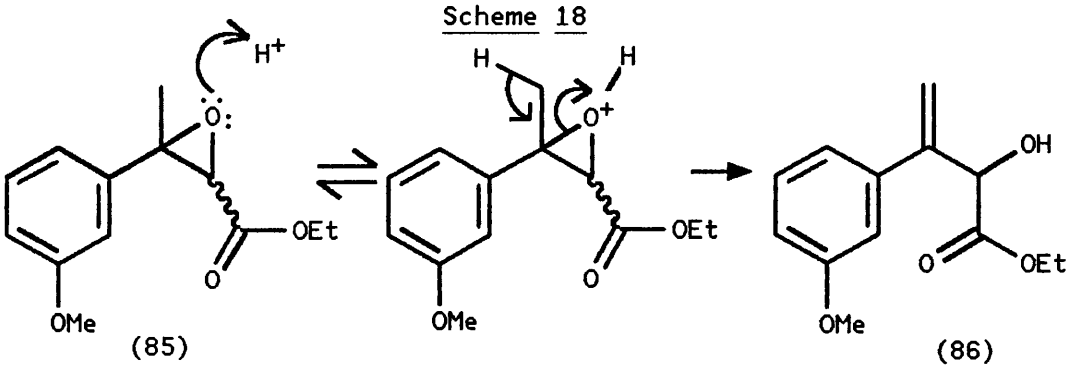


In our hands, synthesis of the aldehyde[28] (88) was attempted by several other routes, however none of those tried gave a better

yield on scaling up than the literature route. This employs a Darzen's glycidic ester reaction, followed by ring opening of the epoxide, hydrolysis of the ester and subsequent decarboxylation of the corresponding acid (87). (These steps are shown in Scheme 17.)

Ring opening of the epoxide was carried out by stirring it in ether containing a few drops of concentrated sulphuric acid. This gave the ester (86) (see Scheme 18), which was hydrolysed to the

Scheme 18

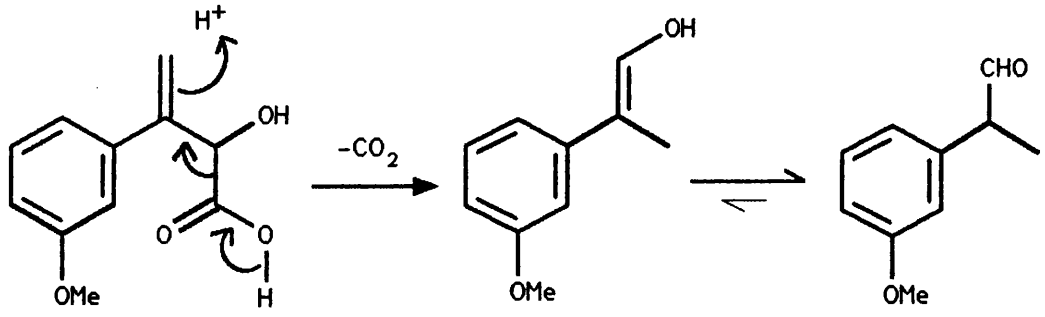


(85) (86)

free acid using aqueous 2M sodium hydroxide solution.

Steam distillation of the product acid (87) in 3M sulphuric acid effected decarboxylation, yielding the required aldehyde (88). Since this compound is prone to side reactions steam distillation also has the advantage of removing it from the reaction mixture. The probable mechanism for the decarboxylation is shown in Scheme 19. An overall

Scheme 19



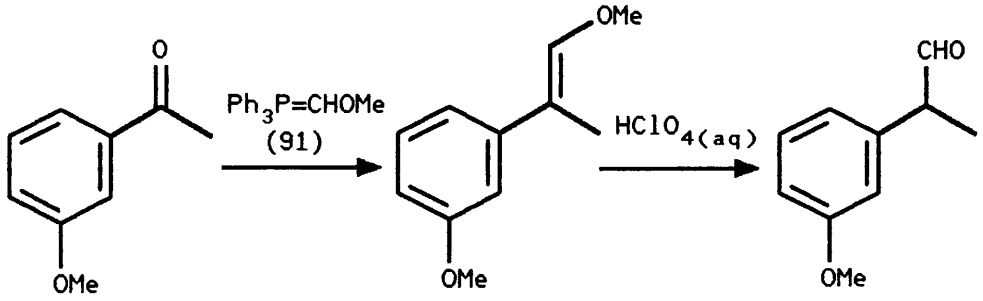
(87) (88)

yield of 30% was obtained for the aldehyde (88) (on a one molar

scale).

Another route tried involved the use of a Wittig reaction with the ylid (91), followed by demethylation by perchloric acid (see Scheme 20). This gave the aldehyde (88) in a 27% yield when performed on a small scale, but on scale up the by-product, triphenylphosphine oxide, was difficult to remove and contaminated subsequent compounds in the synthetic chain.

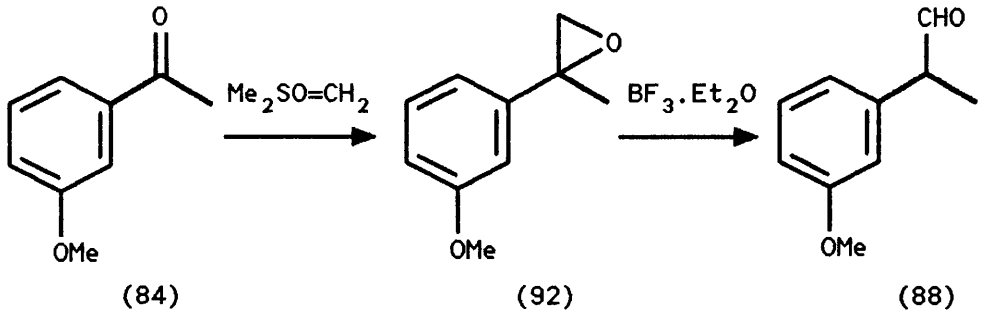
Scheme 20



(84) (90) (88)

Rearrangement of the epoxide (92) with boron trifluoride-etherate was also investigated as a method of synthesising the aldehyde (88). (See Scheme 21.) The epoxide was formed in a 52% yield by reacting the acetophenone (84) with Corey's sulphonium reagent.[29] Scaling up led to reduced yields.

Scheme 21

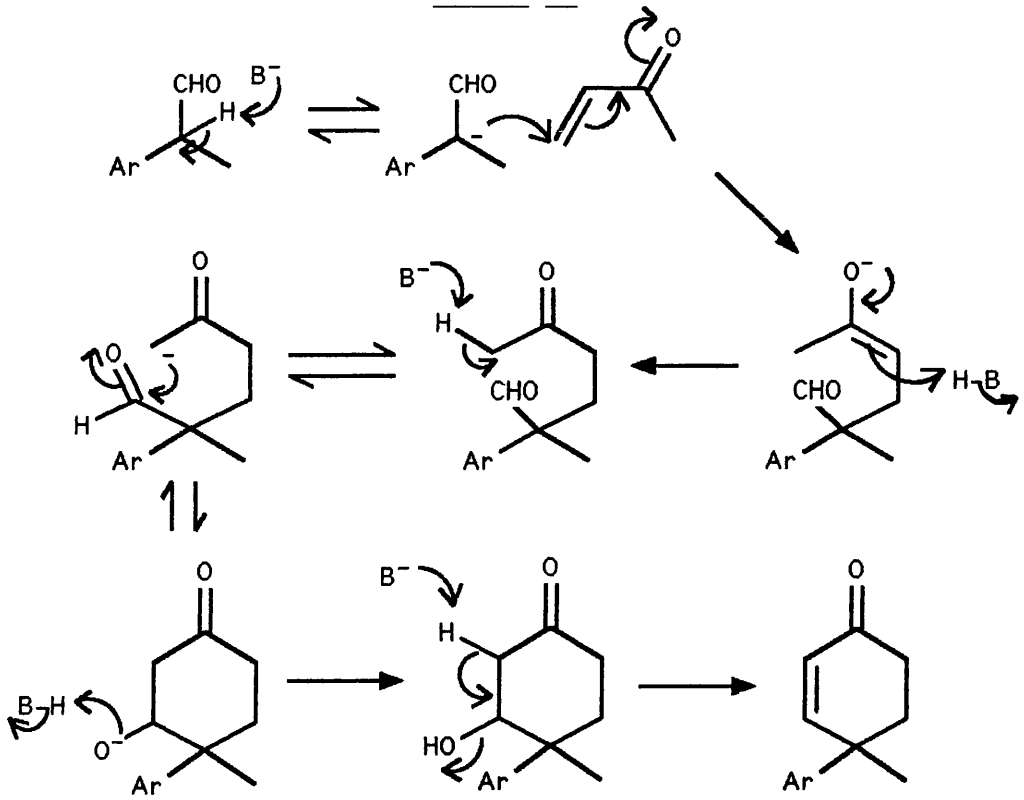


(84) (92) (88)

The Robinson annulation of the aldehyde (88) with methyl vinyl ketone was performed using benzyl trimethyl ammonium hydroxide (Triton B) as the base in *t*-butanol. The mechanism of the reaction

(see Scheme 22) involves a Michael type addition, followed by an aldol condensation.

Scheme 22

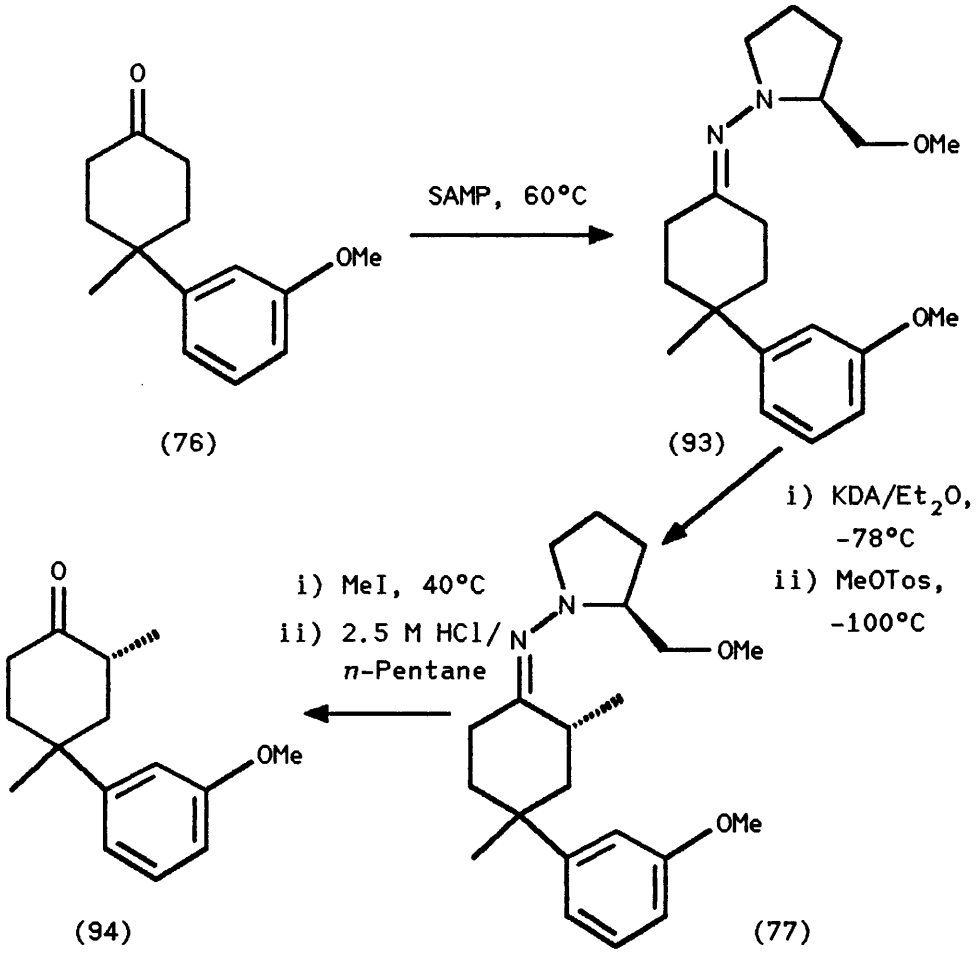


Hydrogenation of the cyclohexenone (89), over a palladium on charcoal catalyst in glacial acetic acid, gave the cyclohexanone (76) in a 65% overall yield for the two steps.

2.2.2 The Chiral Alkylation of the Cyclohexanone (76)

Of the various methods suitable for chiral alkylation of the cyclohexanone (76),[30] the method of Enders,[26] utilising the chiral hydrazone derived from (*S*)-1-amino-2-methoxymethylpyrrolidine (SAMP) was chosen. The Ender's method has a good reputation, and high enantiomeric excesses have been reported for the alkylation of analogous compounds. It also has the advantage that the chiral auxiliary may be recovered. (See Scheme 23.)

Scheme 23



Hydrazone formation was a reasonably facile procedure, which entailed heating the cyclohexanone (76) and SAMP at 60°C, under argon, for 18 h. Purification by distillation gave the chiral hydrazone (93) as a colourless oil in 90% yield. The mixture of the two

diastereomers produced gave rise to complicated ^{1}H n.m.r. and ^{13}C n.m.r. spectra that could not be readily assigned. However, the mass spectrum of the isomers showed the expected mass ion peak at *m/z* 330 and the elemental analysis fitted the required formula.

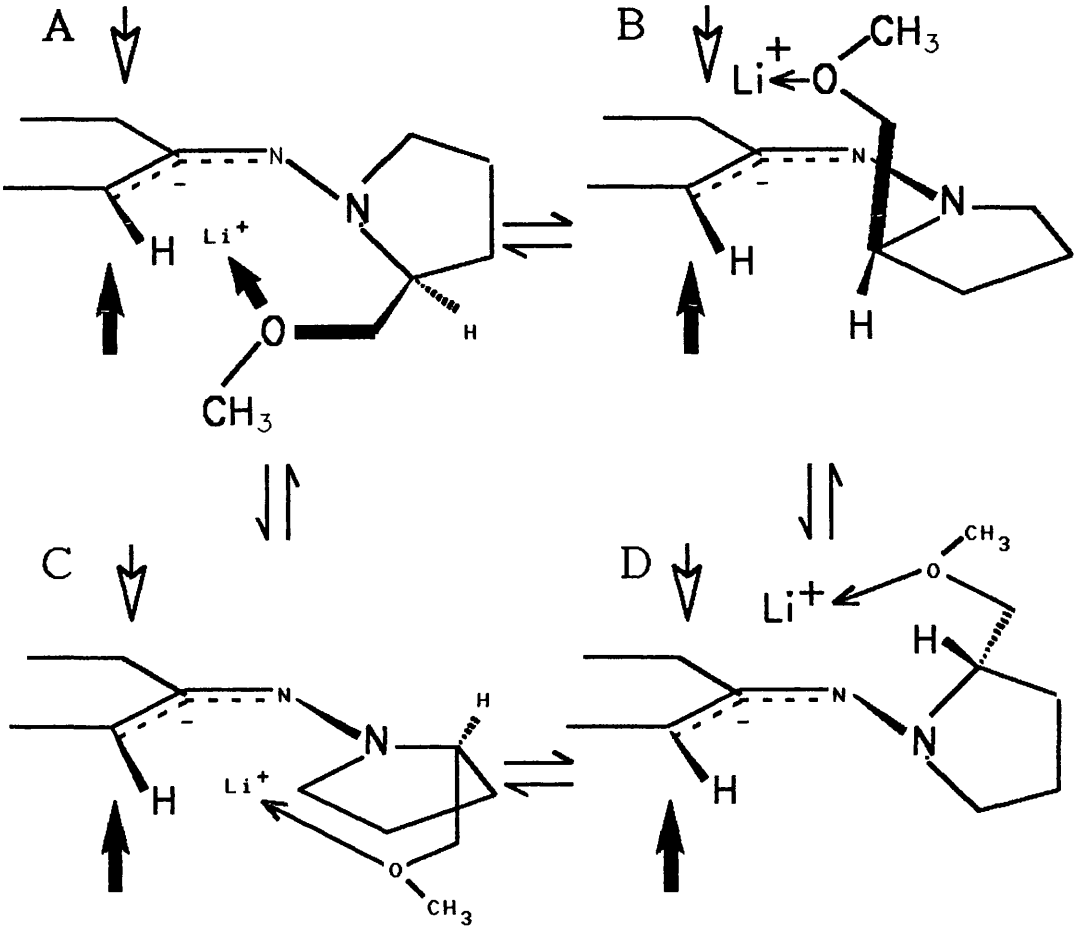
The chiral hydrazone (93) was then metalated using potassium diisopropylamide[31] (KDA) in dry ether at -78°C. KDA reacts at a faster rate than lithium diisopropylamide (LDA). This is despite the fact that LDA can be used at 0°C, whereas KDA must be used at -78°C to avoid its decomposition. Even with KDA complete metalation was never achieved because of the slow rate of the reaction, possibly the result of steric hindrance. For practical reasons, it was only possible to keep the suspension at -78°C for 8 h before quenching. In the case of LDA, a gum was formed on stirring at room temperature. Given a cold room with the necessary facilities, or a cryogenic bath, it would presumably be possible to extend the reaction time to ensure that complete metalation had occurred.

The reaction was quenched at -100°C, using an ethereal solution of methyl tosylate, and the temperature was maintained at -100°C for a further hour. Both low temperature[26] and the use of a bulky alkylating reagent[32] have been shown to increase the enantiomeric excess of the chirally alkylated product.

Enders' chiral hydrazone method of chiral induction relies on one of the four possible conformers of the metalated hydrazone being more thermodynamically stable than the others. (See Figure 6.)

Electrophiles predominantly attack the metalated hydrazone from below the CCNN plane (indicated by the black arrow). For conformations A and D, this would mean that electrophilic substitution was occurring *syn* to the co-ordinated lithium (S_Ei), whereas

Figure 6

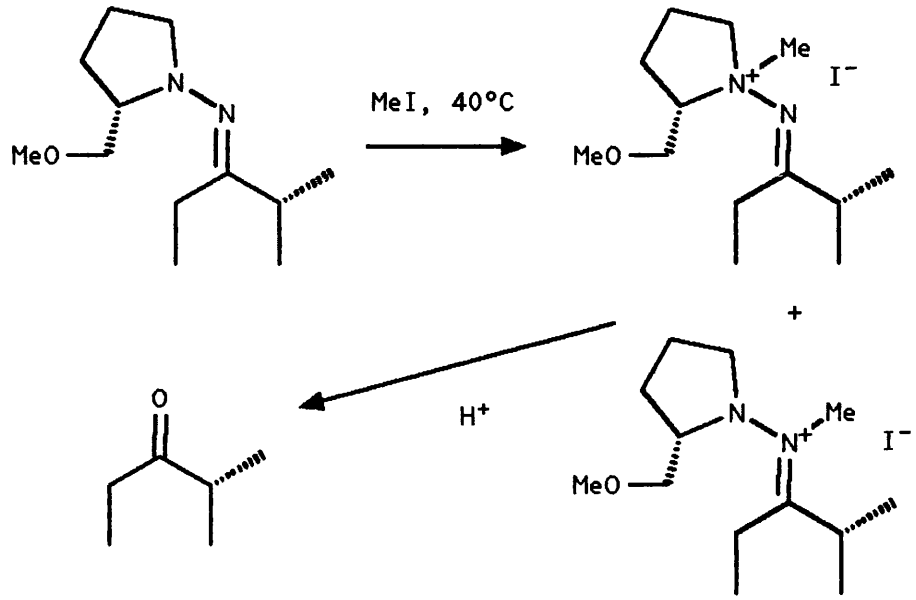


conformations B and C would require an electrophilic substitution *anti* to the co-ordinated lithium. Inspection of molecular models (CPK, Dreiding) favours conformation A, which is in full agreement with the experimental results and calculations described by Enders.[26]

The CN double bond of the crude chirally alkylated hydrazone (77), (mainly of a mixture of two stereo and two diastereomers: *ERR*; *ERS*; *ZRR* and *ZRS*), was then cleaved to give the chiral dimethylcyclohexanones, (78) and (79). This was effected by heating the hydrazone (77) in a pressure tube at 40°C with methyl iodide. The methiodide salt so formed was then hydrolysed directly in a biphasic system of *n*-pentane and 2.5 M hydrochloric acid. A mixture of the chiral dimethylcyclohexanones, (78) and (79), was obtained as a

colourless oil. (See Scheme 24.)

Scheme 24

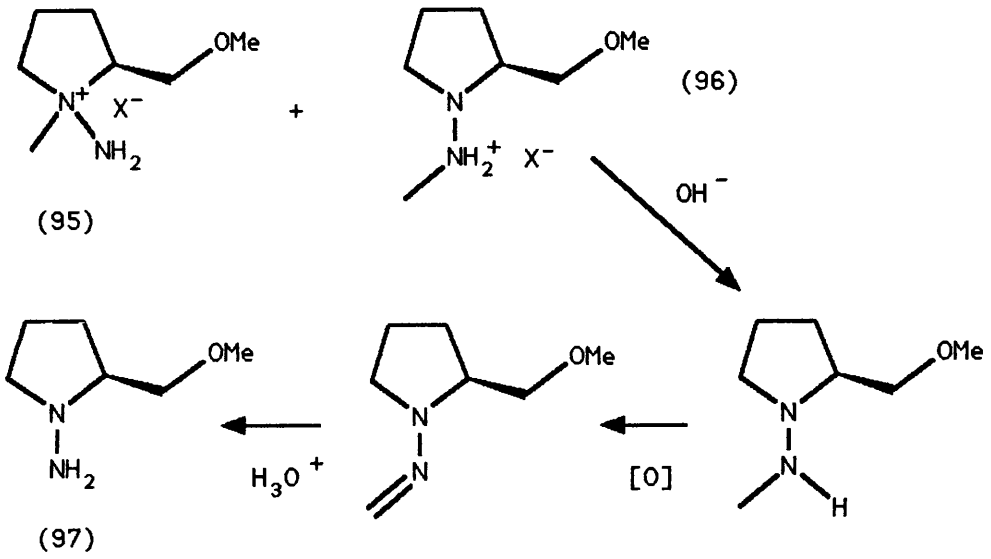


Chiral α-alkylated ketones rapidly racemise in the presence of traces of base, but are more stable in the presence of acid. Biphasic acid hydrolysis therefore, minimises racemisation of the product. Low solubility of the acid in the *n*-pentane layer, in which the chiral dimethylcyclohexanones, (78) and (79), accumulate, also aids in the prevention of racemisation. Previous studies[26] had shown that no noticeable racemisation occurs in chiral ketones in this system over a period of 1 h.

A 40% recovery of the SAMP using this method was referred to by Enders[26] as a part of a Ph.D. dissertation by Eichenauer,[33] but no published description of the procedure is available. Our attempt involved basification of the aqueous phase, which contains the two salts, (95) and (96), followed by implementation of the steps illustrated in Scheme 7. The results were far short of those claimed by Enders.

As a consequence of the base sensitivity of the chiral dimethyl-cyclohexanones, (78) and (79), all glassware had to be acid washed

Figure 7



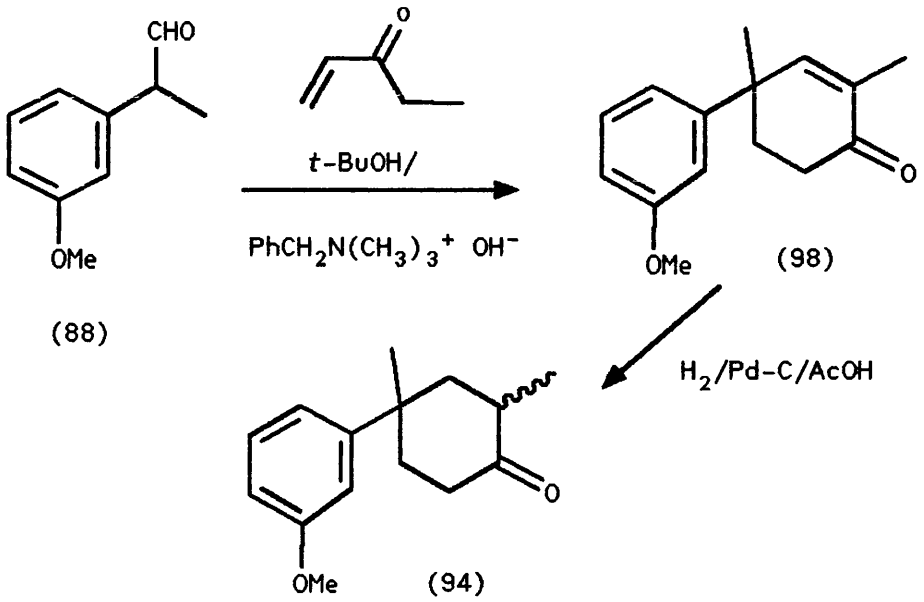
prior to use, in further work. Purification by column chromatography on silica gave the two separate diastereomers in a *cis/trans* ratio of 1:3 and a combined yield of 61%. A diastereomeric excess (d.e.) of 96% was obtained for the *trans*-dimethylcyclohexanone (78), which was determined by gas chromatography and also from the ^1H n.m.r. spectrum. If the chiral dimethylcyclohexanone (78) was undergoing epimerization on the silica during chromatography the d.e. would be expected to be substantially lower.

Hydrazone cleavage was also attempted using Enders' standard conditions for the ozonolysis of the CN double bond. However, on distillation of the resultant product, decomposition took place leaving a black tar and very little of the desired product.

Determination of the enantiomeric excess of the *trans*-dimethylcyclohexanone (78) was made using the chiral solvating agent (-)-1-(9-anthryl)-2,2,2-trifluoroethanol (TFAE) in a ^1H n.m.r. experiment. Racemic *trans*-dimethylcyclohexanone (78) was used as a control. The racemate was prepared by performing a Robinson annulation on the aldehyde (88) using ethyl vinyl ketone (EVK) and

then hydrogenating the methylcyclohexenone (98) over palladium on charcoal catalyst. (See Scheme 25.)

Scheme 25

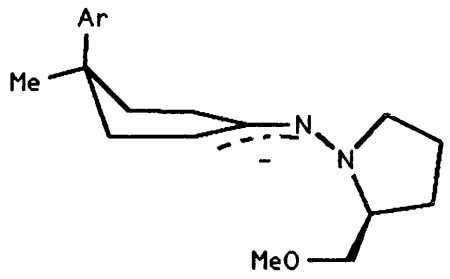


The enantiomeric excess of the *trans*-dimethylcyclohexanone (78) was found to be 76% (±2%). Unfortunately, the chiral solvating agent did not resolve the peaks in the ^1H n.m.r. spectrum of the racemate of the *cis*-dimethylcyclohexanone (79). Consequently it was not possible to measure the enantiomeric excess until the oxime of the *cis*-dimethylcyclohexanone (101) had been synthesised. No decrease in the enantiomeric excess was observed on the formation of the *trans*-oxime (102); therefore it may be reasonably assumed that the same is true for the formation of the *cis*-oxime (101). This being the case, the enantiomeric excess of the *cis*-dimethylcyclohexanone (79) can be deduced to be the same as that of the *cis*-oxime (101) (60 ± 4%) using the chiral solvating agent TFAE (see Chapter 2.2.3).

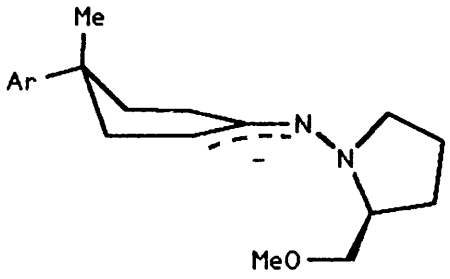
The difference in the enantiomeric excesses of the two diastereomers can be explained by the difference in the relative conformational energies of the metalated hydrazone (see Figure 6),

depending on whether the aromatic ring occupies a pseudo-axial or a pseudo-equatorial position. (See Figure 8.)

Figure 8



(99)



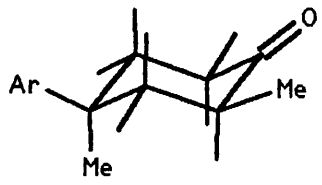
(100)

Assignment of the ^1H n.m.r. spectra of the *cis*- and *trans*-dimethylcyclohexanones, (79) and (78), was made with the aid of n.O.e. studies, and from the spin-spin splitting patterns and associated coupling constants. (A brief discussion of the factors involved is given in the next chapter in the assignment of the *cis*- and *trans*-oximes, 101 and 102.) The appearance of the resonance of the 3-H proton as a triplet means that it has two large coupling constants, one geminal and one vicinal-diaxial, and thus the 3-H proton must be axial with respect to the ring. In the spectrum of the *trans*-dimethylcyclohexanone (78) the resonance of the 5-H axial proton is clearly visible adjacent to the resonance of the 3-H proton. It is seen as a triplet of doublets, with two large coupling constants and one smaller coupling constant. Occurring at an analogous position in the ring to the 3-H proton, the resonance of the 5-H_{ax} proton has a similar chemical shift and splitting pattern.

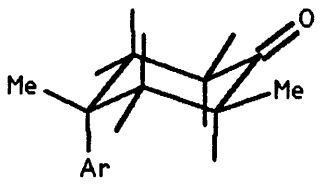
In the case of the *cis*-dimethylcyclohexanone (79), irradiation of the 4-CH_3 resonance at δ 1.59 ppm led to an enhancement of the resonances of the 2-H_{ax} and 6-H_{ax} protons, providing evidence that the 4-CH_3 group is in an axial position on the cyclohexanone ring

(see Figure 9). Irradiation of the 2-CH_3 resonance in both the *cis*-

Figure 9



(79)

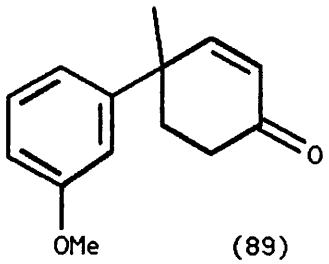


(78)

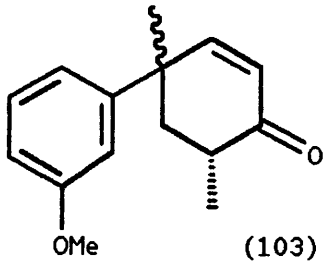
and *trans*-dimethylcyclohexanones, (79) and (78), at δ 1.0 ppm, resulted in an enhancement of the resonances of the 2-H_{ax}, 3-H_{ax} and 3-H_{eq} protons, which suggests that the 2-CH_3 group occupies an equatorial position in both compounds. If the 2-CH_3 were in an axial configuration, an enhancement of the 2-H_{eq}, 6-H_{ax} and 3-H_{eq} protons would be expected. (An X-ray crystallographic determination of the *cis*-dimethylcyclohexanone oxime (101) confirmed the above configurational assignment.)

The chiral alkylation was also performed on the cyclohexenone (89) (see Figure 10), which gave a poor yield, but the same enantiomeric excess. However, separation of the two diastereomers proved impossible for the dimethylcyclohexenones (103).

Figure 10



(89)

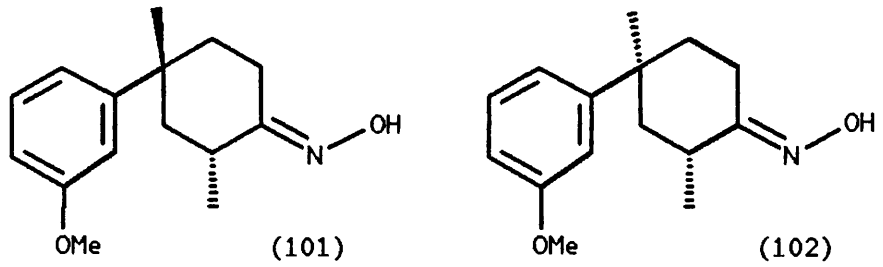


(103)

2.2.3 The Beckmann Rearrangement

The two diastereomers of the chiral dimethylcyclohexanone, (78) and (79), were converted into their respective oximes immediately after isolation, in order to minimise racemisation. Oxime formation was performed by stirring the dimethylcyclohexanones, (78) and (79), with hydroxylamine hydrochloride and sodium acetate in aqueous methanol at room temperature for 24 h. The oximes, (101) and (102), were

Figure 11



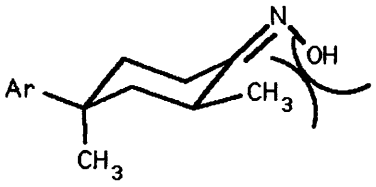
(101) (102)

obtained as colourless crystalline solids in 85% yield after recrystallization. From a ^1H n.m.r. experiment using the chiral solvating agent TFAE, the enantiomeric excess of the *trans*-oxime (102) was determined to be 76% (±2%). This means that the amount of racemisation taking place during the oxime formation was negligible. Using the same technique, the enantiomeric excess of the *cis*-oxime (101) was determined to be 60% (±4%).

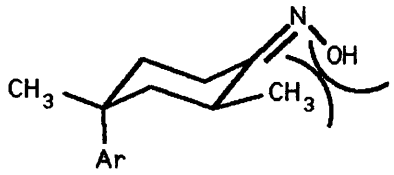
In both cases the oximes, (101) and (102), were found to consist solely of their *E*-isomers with respect to the CN double bond. The reason for this *E*-selectivity is presumably that the methyl group at C-2 occupies an equatorial position in both cases (see Figure 12). Therefore the *Z*-oximes would experience an unfavourable steric interaction between the hydroxy group and the 2-CH_3 group.

The structure of the *cis*-oxime (101) was confirmed by X-ray crystallography. (See Figure 13.)

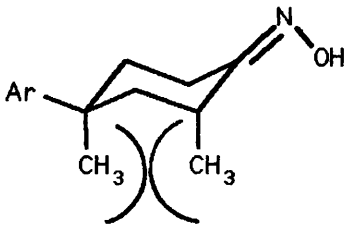
Figure 12



(104)



(105)



(106)

Assignment of the ^1H n.m.r. spectra of the two oximes was made on the basis of the spin-spin splitting patterns and associated coupling constants. In a cyclohexane chair conformation the coupling constants between the adjacent protons can be roughly calculated using the Karplus equation, which relates the size of the coupling constant to the dihedral angle (see Figure 14).

The coupling constant of two geminal protons and that of two adjacent axial protons will tend to be large (J = 10-15 Hz), whereas the coupling constant of one axial proton and an adjacent equatorial proton are usually medium to small in value ($J \approx 5$ Hz). The smallest coupling constant is that between two adjacent equatorial protons (J = 0-3 Hz).

For the *trans*-oxime (102) the resonance of the H-3 axial proton has two large coupling constants (one geminal and one vicinal diaxial) giving a "triplet" at δ 1.43 ppm, J = 13.3 Hz. The resonances of the H-5 axial and H-6 axial protons occur as two quartets of doublets,

Figure 13

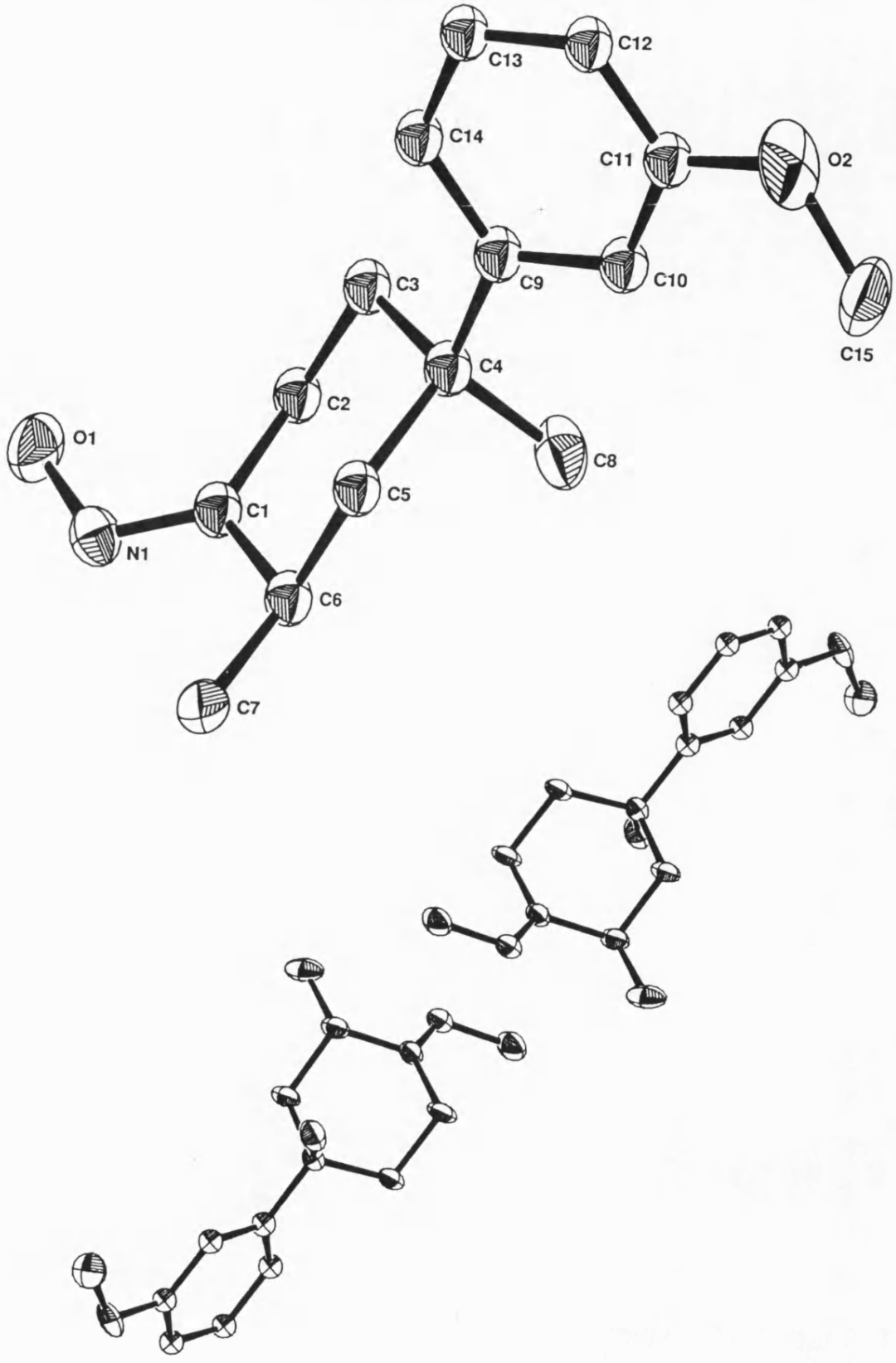
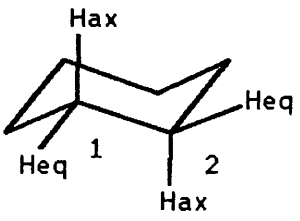


Figure 14



$J_{a1,e1}$ = large (geminal)

$J_{a2,e2}$ = large (geminal)

$J_{a1,a2}$ = large

$J_{a1,e2} \approx J_{e1,a2}$ = medium-small

$J_{e1,e2}$ = small

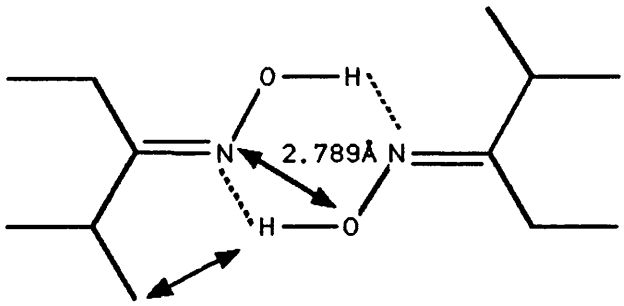
with two large coupling constants (one geminal and one vicinal diaxial) and one smaller coupling constant (a vicinal axial-equatorial coupling) at δ 1.82-1.49 ppm. Resonances for the H-2 axial proton and the two H-5 and H-3 equatorial protons are multiplets lying at δ 2.38-2.20 and δ 2.50-2.38 ppm respectively. The resonance due to the H-6 equatorial proton occurs at relatively low field, δ 3.27 ppm, as a doublet of triplets, J = 14.1 and 2.8 Hz. Presumably this proton is being deshielded by the electronic effect of the oxygen atom, which lies comparatively near in space (2.29Å calculated from the X-ray data for the *cis*-oxime, 101).

The ^{1}H n.m.r. of the *cis*-oxime (101) is similar to that of the *trans*-compound, except that the resonances of the H-3 equatorial, H-6 axial and H-5 protons now all overlap and are seen as a multiplet at δ 2.10-1.75 ppm.

A n.O.e. study on the *trans*-oxime (102), irradiating the exchangeable resonance of the OH proton at δ 9.3 ppm, gave signal enhancements for the methyl group at C-2 of 4.1%; the H-2 axial proton of 0.7% and the H-6 axial proton of 1.2%. This apparently contradictory evidence for the *E/Z*-configuration of the oxime is explained by looking at the X-ray structure of the *cis*-oxime (101). On examining the intermolecular distances of the atoms (see Figure 15)

it can be seen that the distance between the nitrogen and oxygen atoms in the oxime functionality in adjacent molecules (2.79Å), is less than the combined Van der Waals radii of the oxygen and nitrogen atoms (2.90Å).[34] This observed distance of 2.79Å implies that the oxime is hydrogen bonded and agrees with the intermolecular distances found in other known examples of hydrogen bonded oximes.[34] The absorption of the hydroxy group in the infrared spectrum occurs as a broad peak at 3250 cm^{-1}, which is again indicative of hydrogen bonding.

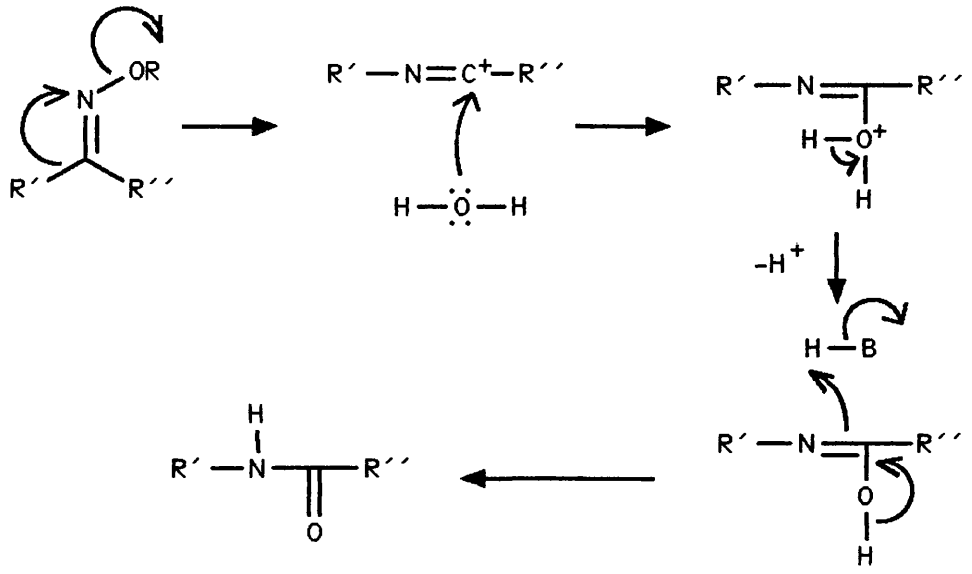
Figure 15



Hydrogen bonding would lead to the geometry seen in Figure 15, where the proton of the oxime hydroxyl is relatively near in space to the methyl group at C-2 on the neighbouring molecule, which would account for the magnitude of the n.O.e. obtained. It is possible that when in solution, the oxime exists in a dimeric form similar to that encountered in carboxylic acids.

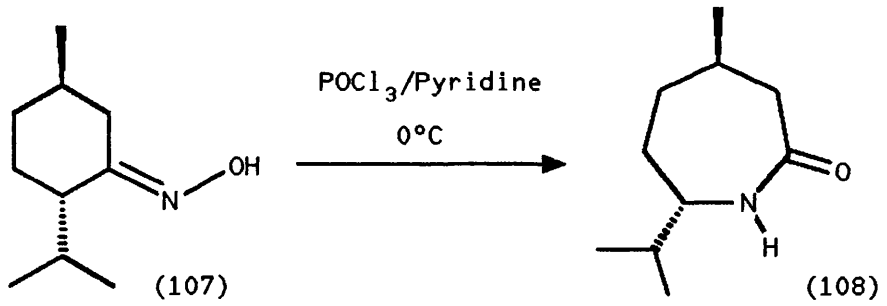
The Beckmann rearrangement involves the rearrangement of an oxime to an amide. The hydroxyl group is converted to a leaving group and the alkyl group *trans* to the modified hydroxyl group migrates to the nitrogen atom displacing the leaving group. This leaves a positive charge on the carbon atom, which is rapidly attacked by water, eventually affording an amide unit. (See Scheme 26.)

Scheme 26



Perez and Fernandez[35] have shown that it is possible to effect the rearrangement of the oxime (107) to the amide (108) without racemisation (see Scheme 27). The reagent used was phosphorus oxychloride/pyridine and it is noteworthy that the bulky isopropyl group determined the formation of the *E*-oxime from the parent ketone.

Scheme 27



(107) (108)

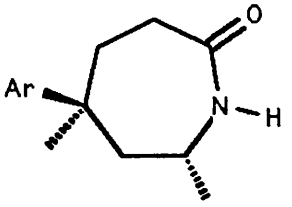
Perez and Fernandez found that by reacting the chiral oxime (107) with phosphorus oxychloride in pyridine at 0°C,[36] the only observed product was the caprolactam (108). The bulky isopropyl group led to the sole formation of the *E*-isomer, which in turn gave rise to the single caprolactam isomer produced under the above

conditions.

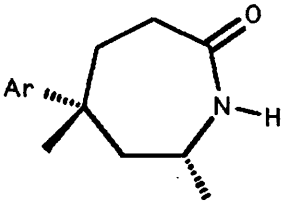
By applying this procedure to the *trans*- and *cis*-dimethyl-cyclohexanones, (78) and (79), the respective caprolactams, (109) and (110), were obtained exclusively, as colourless crystalline solids, in 70-80% yields after recrystallization.

^{1}H n.m.r. studies, using the chiral solvating agent TFAE, showed that no racemisation had occurred in the formation of the *trans*-caprolactam (109). Indeed, the enantiomeric excess was improved by means of the recrystallization.

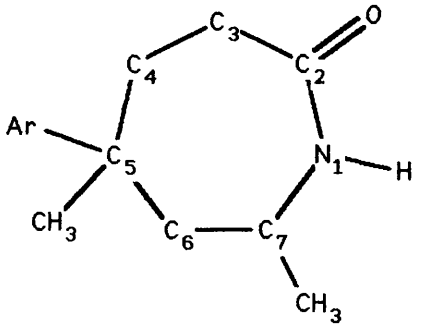
Figure 16



(109)



(110)

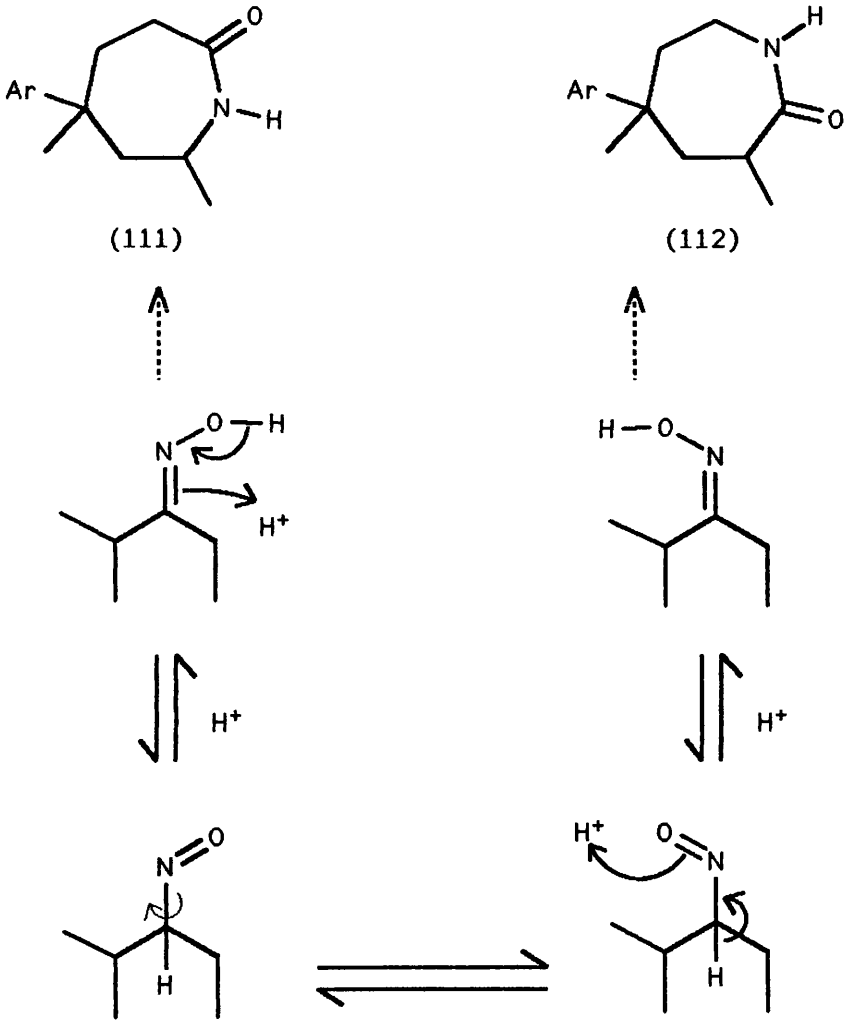


Assignment of the ^{1}H n.m.r. was made with the aid of an irradiation study. In the case of the *trans*-caprolactam (109), irradiation of the resonance of the H-7 proton, a multiplet at δ 3.48 ppm, led to the collapse of a doublet of doublets at δ 1.58 ppm to a doublet, showing that this signal was the resonance of one of the H-6 protons. Irradiation of a signal at δ 1.58 ppm caused the doublet under the multiplet at δ 2.48 ppm to collapse to a singlet, revealing it to be the resonance of the other H-6 proton. The resonances of the

final four protons in the caprolactam ring were assigned on the basis that the H-3 protons occur at a lower field due to the deshielding effect of the adjacent carbonyl group of the amide. Thus the resonances of the remaining three protons in the multiplet at δ 2.4 ppm may be assigned to the two H-3 protons and one of the H-4 protons. Finally, the multiplet at δ 1.66 ppm was assigned to the resonance of the other H-4 proton. Since the resonances of H-4 and H-6 occur at similar chemical shifts, they may be on the same face of the caprolactam ring.

An alternative method for the Beckmann rearrangement, which involved heating the cyclohexanone with hydroxylamine-*O*-sulphonic acid in formic acid[37] gave an inseparable mixture of the two possible regioisomers, (111) and (112). This can be explained by the equilibrium between the *E*- and *Z*-isomers that is known to take place in acid conditions[38] leading to the rearrangement of the *Z*- as well as the *E*-oxime. (See Scheme 28.)

Scheme 28

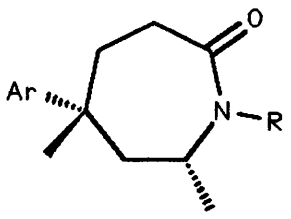


2.2.4 *N*-Protection and Ring Opening of the Caprolactam (110)

When considering the protecting group for the caprolactam, we were looking for a group that fulfilled two primary conditions. These were that it would not be attacked preferentially by alkyl lithium reagents in the amide cleavage step and also that it would be easily removed at the end of the synthesis.

In our initial studies we investigated carbamates as possible protecting groups, relying on the more reactive nature of the amide carbonyl compared to that of the carbamate to give the required selectivity on ring opening. Benzyl chloroformate was reacted with the *cis*-caprolactam (110) using a variety of conditions to give the benzylcarbamate derivative (113) in varying yields. The best results were obtained by stirring a solution of the *cis*-caprolactam (110) in tetrahydrofuran, with sodium hydride, at room temperature for 1 h and then heating the resultant solution under reflux conditions for 8 h. Using this method the benzylcarbamate derivative (113) was obtained in 49% yield, with a 19% recovery of starting material.

Figure 17



R = H (110), CO_2CH_2Ph (113), CH_2Ph (114) and CH_3 (116).

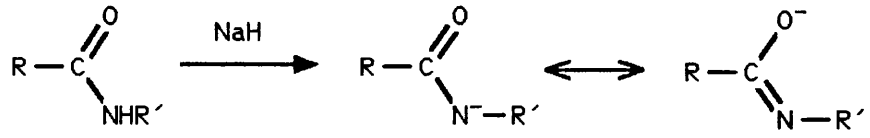
By way of comparison the *cis*-caprolactam (110) was stirred with sodium hydride at room temperature, in tetrahydrofuran, for 1 h and then treated with benzyl bromide. After stirring at room temperature for 16 h the benzylcaprolactam (114) was obtained in 51% yield, together with a 25% recovery of starting material. By employing identical reaction conditions, but this time using methyl iodide to

quench the amide anion formed, the methylcaprolactam (116) was isolated quantitatively. When this reaction was repeated on the *trans*-caprolactam (109), it was found that the initial deprotonation of the amide required 24 h to reach completion. However, on quenching with methyl iodide the yield was also quantitative.

As a consequence of these results, we decided to use a methyl group as the protecting group for the ring opening reaction. Deprotection of *N*-methyl derivatives of various opioid derivatives are well documented in the literature. Reagents in common use for this reaction include cyanogen bromide and several chloroformates.

The carboxamide anion involved in the alkylation/acylation of amides under basic conditions[39] possesses two centres at which electrophilic attack is possible. (See Scheme 29.)

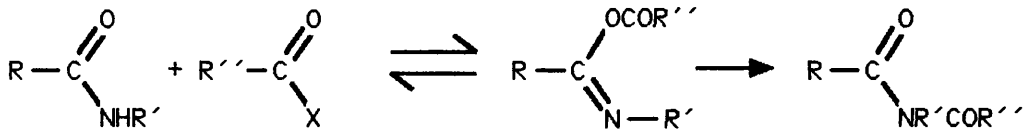
Scheme 29



Alkylation/acylation can take place at either the oxygen or the nitrogen atom. In practice, the alkylation of primary and secondary amides in the presence of strong base normally occurs at the nitrogen atom. In the presence of silver salts and also by using alkyl diphenyl sulphonium salts, the *O*-alkylated products predominate.[40] Acylation of amides under neutral conditions is thought to proceed *via* an *O*-acylated intermediate[41] to give the *N*-acylated product. (See Scheme 30.) However, under the basic conditions used, acylation probably involves direct attack of the nitrogen anion, as is the case for alkylation.[42]

The observed difference in the yields of the three *N*-protected

Scheme 30



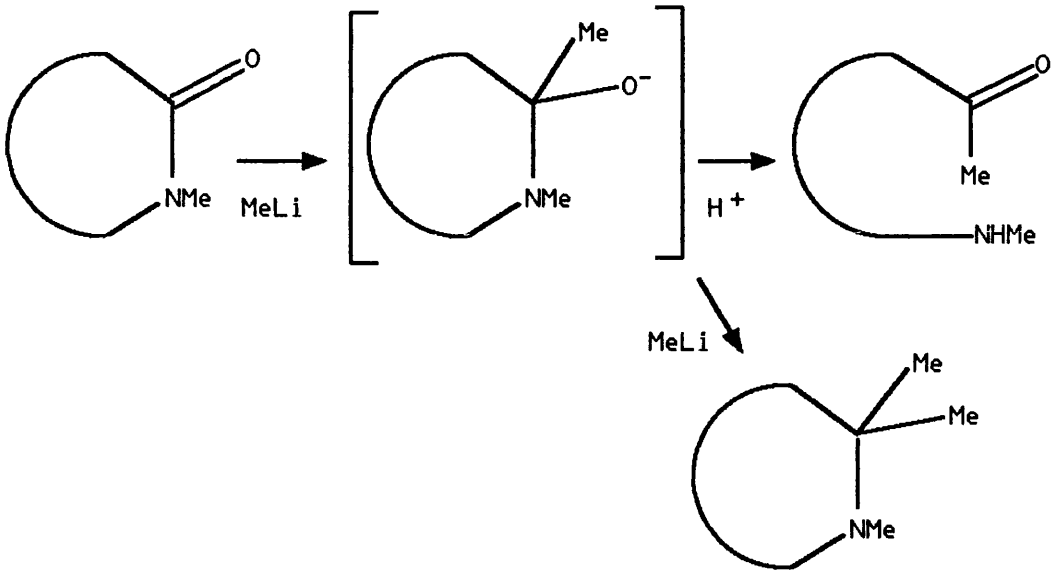
compounds can be attributed to steric factors influencing the attacking electrophiles. The fact that the amide is being fully deprotonated by the sodium hydride is evident from the quantitative yields obtained when quenching with methyl iodide.

The ^1H n.m.r. spectra of the *trans*- and *cis*-methyl-caprolactams, (115) and (116), show the resonance of the *N*-methyl protons as a singlet at around δ 2.9 ppm and the disappearance of the resonance of the exchangeable N-H proton at around δ 6.1 ppm. These spectra were assigned with the aid of two dimensional COSY-90 ^1H n.m.r. experiments.

Ring opening of the caprolactam was performed by adding methyl lithium, at 0°C, in dry tetrahydrofuran. Methyl lithium attacks the amide carbonyl group to give a tetrahedral intermediate which then collapses to give the aminoketone when quenched in aqueous acid. (See Scheme 31.) In the case of the *cis*-methylcaprolactam (116), this gave the methylaminoketone (117), in a 53% yield, as a yellow oil, which was relatively unstable in air and decomposed on silica. When the reaction mixture was quenched with trifluoroacetic anhydride, the trifluoroacetamidoketone (81) was isolated in 55% yield, as a pale yellow waxy solid, with a 13% recovery of starting material.

Only one equivalent of methyl lithium was used, in order to minimise over reaction which could occur if a second molecule of methyl lithium attacked the carbonyl centre. This side reaction would give rise to the dimethyl compound (see Scheme 31) and is a known

Scheme 31



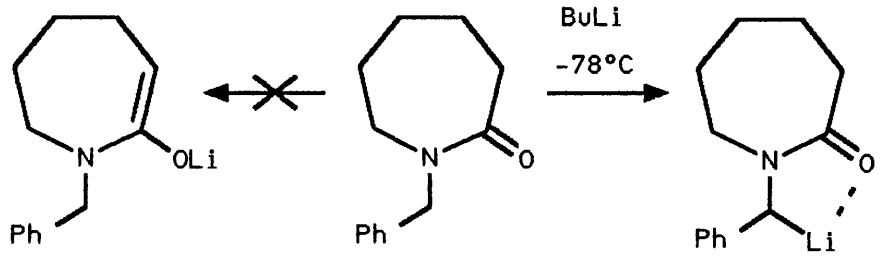
product when methyl Grignard reagents are added to *N*-methyl-caprolactam.[43] Increasing the amount of methyl lithium added did indeed lead to a decrease in yield, however, the dimethyl compound was not isolated.

The change in functionality from amide to aminoketone can clearly be seen by comparing the IR spectra of the methylcaprolactam (116) and the aminoketone (117), in which the absorption peak of the carbonyl changes in wavenumber from 1640 cm^{-1} to 1695 cm^{-1}. These values are typical for the carbonyl absorption of a seven membered lactam and an aliphatic ketone respectively. The change in functionality is also visible in the ^1H n.m.r. spectrum of the methyl amino ketone (117) in which the appearance of a singlet at δ 2.03 ppm (due to the resonance of the H-1 protons) reveals the presence of the methyl ketone. An upfield shift of the *N*-methyl resonance from δ 2.90 ppm in the starting material to δ 2.25 ppm in the product also illustrates the change from amide to amine functionality of the nitrogen atom.

The ^{1}H n.m.r. spectrum of the trifluoroacetamidoketone (81) is complicated by the fact that it is present as a 1:9 mixture of rotomers. This made precise assignment of all the proton resonances, and also of the ^{13}C n.m.r. spectrum, impossible. However, the compound analysed correctly and the two carbonyl peaks of the ketone (1710 cm^{-1} sh) and the trifluoroacetamide (1680 cm^{-1}) were clearly visible in the IR spectrum.

Ring opening of the benzylcaprolactam (114) with methyl lithium gave only an 8% yield of the benzylaminoketone (118) and a 75% recovery of starting material. This low yield may be attributed to a complex induced proximity effect as described by Meyers and Beak.[44] (See Scheme 32.)

Scheme 32

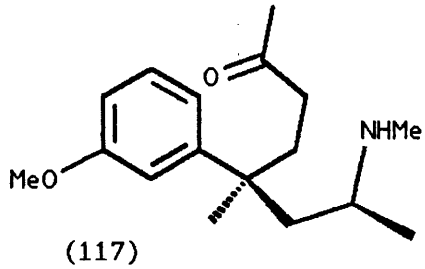


Selective benzylic deprotonation is in competition with the addition reaction and quenching this stabilised anion regenerates starting material.

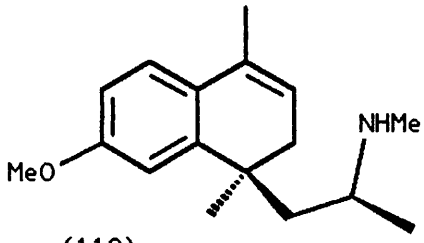
2.2.5 The Cyclodehydration Reaction

Standard reaction conditions, which consisted of heating the aminoketone (117) with polyphosphoric acid at 120°C for 5 minutes,[45] were employed to begin with. This method, however, gave only a 10% yield of the required dihydronaphthalenethanamine (119), as well as a

Figure 18



(117)



(119)

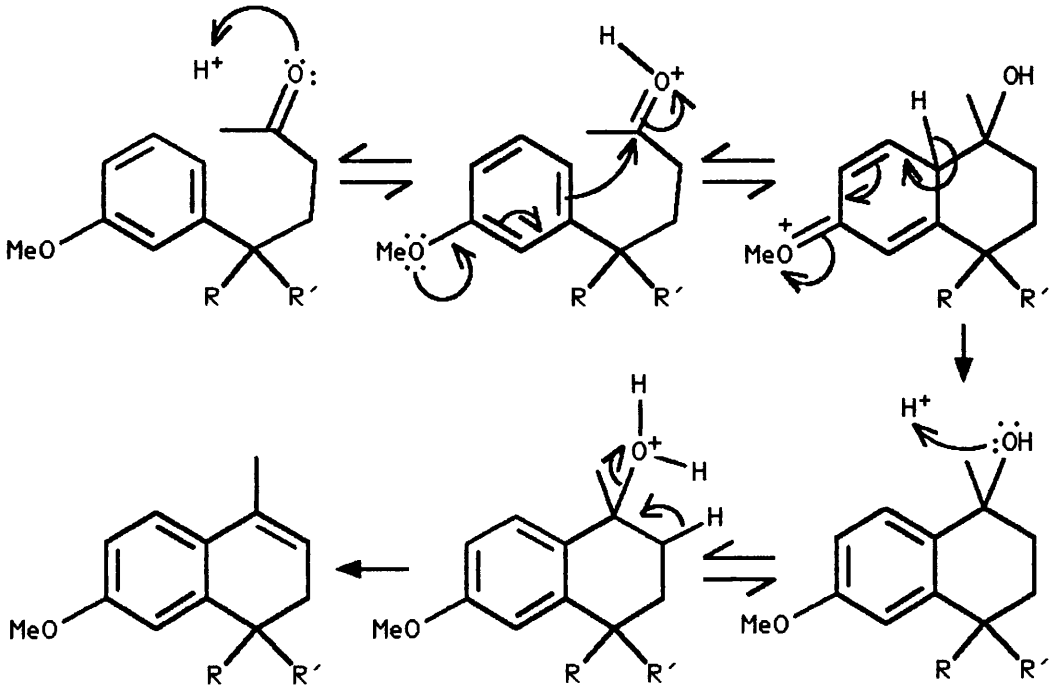
40% recovery of starting material. Presumably the poor yield seen here is due to decomposition of the sensitive aminoketone (117). A milder set of conditions, where the sample is heated in a solution of dioxane with a few drops of concentrated hydrochloric acid, was used by Jackson *et al.*[46] in his modification of the Pomerantz-Fritsch isoquinoline synthesis. By heating a solution of the aminoketone (117) in dry dioxane with a few drops of concentrated hydrochloric acid at 70°C for 6 h, the required dihydronaphthalenethanamine (119) was obtained in 61% yield.

The ^{1}H n.m.r. spectrum clearly shows that the aromatic ring system of this product had changed from being 1,3-disubstituted to 1,2,4-trisubstituted and also shows the appearance of the resonance for the alkenic proton H-3' at δ 5.62 ppm. The pattern of the resonances for the aromatic protons had changed from two triplets and two doublets of doublets to two doublets and a doublet of doublets. Proton resonances were assigned with the aid of a two dimensional COSY-90 ^{1}H n.m.r. experiment. Coupling was observed between the resonance for the alkenic proton H-3' and that of the two

H-2' protons (a multiplet at δ 2.22 ppm). The resonance of the two H-1 protons occurs at δ 1.55 ppm as an ABX quartet, J_{AB} = 14.2 Hz and $J_{AX} = J_{BX}$ = 4.9 Hz, and is coupled to a multiplet at δ 2.47 ppm, which is due to the resonance of H-2. A broad, exchangeable, singlet at δ 1.17 ppm is assigned to the resonance of the amino N-H proton.

The proposed mechanism for the cyclisation reaction involves an initial protonation of the ketone followed by an aromatic electrophilic substitution reaction exclusively at C-6 of the aromatic ring. Subsequent dehydration of the alcohol formed gives the conjugated double bond of the dihydronaphthalene (see Scheme 33). Substitution

Scheme 33



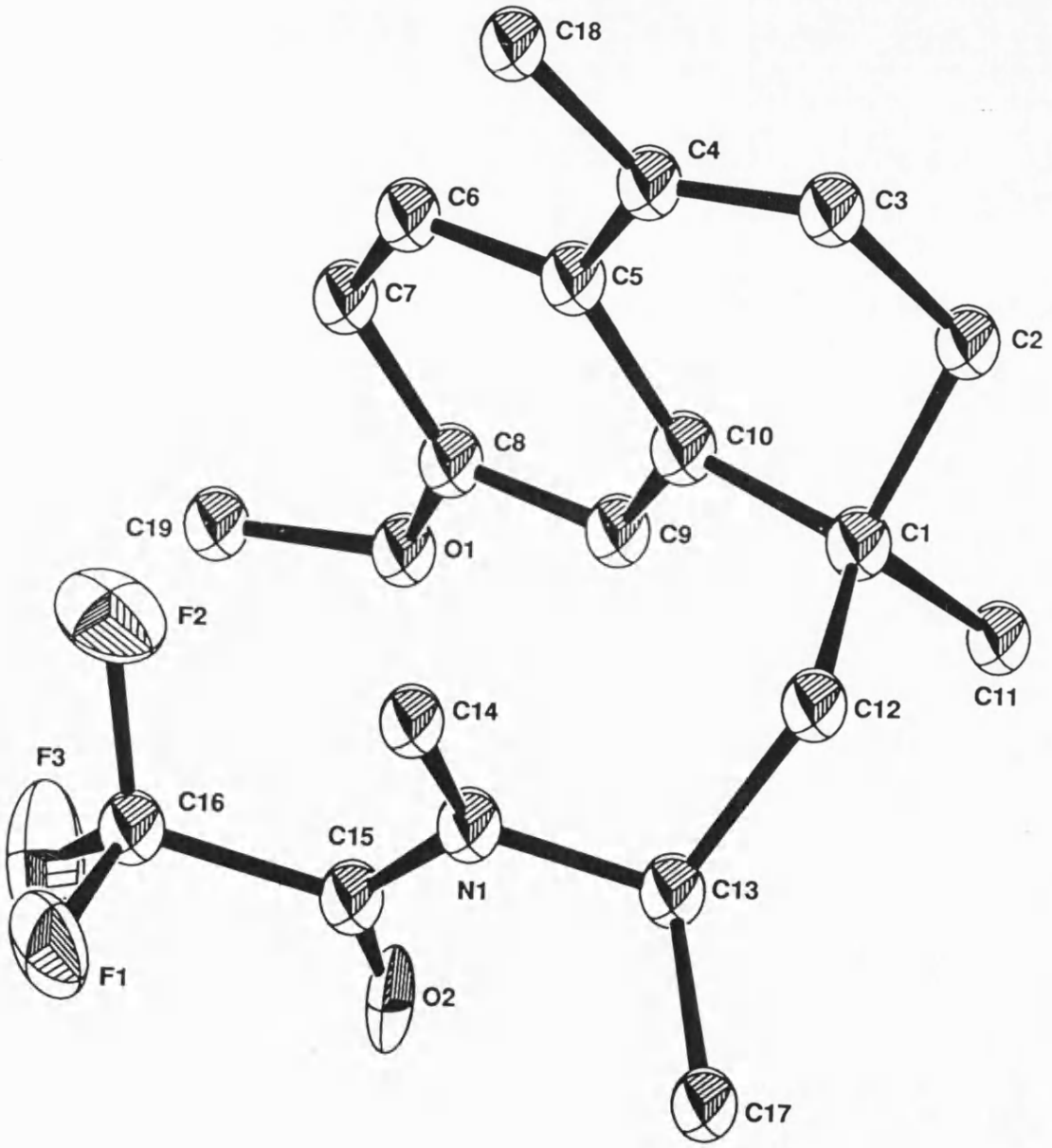
is possible at C-2 of the aromatic ring, but presumably this reaction is disfavoured on steric grounds.

When this reaction was repeated on the trifluoroacetamidoketone (81), the conditions were changed slightly to ensure that the trifluoroacetyl group was not hydrolysed. Moisture was kept to a minimum in the reaction, which was carried out in a solution of

hydrogen chloride in dry dioxane. The only source of water was from the dehydration reaction of the intermediate, which was not enough to cause the hydrolysis of the trifluoroacetamide function to any appreciable extent. The trifluoroacetyl dihydronaphthalenethanamine (120) was obtained in 63% yield, as a colourless crystalline solid (87% based on recovered starting material). ^{1}H n.m.r. revealed that the compound was present as a 1:4 mixture of rotomers. This mixture of rotomers again made assignment of the ^{13}C n.m.r. spectrum impossible. However, all other data are in agreement with the proposed structure, which was confirmed by X-ray crystallography (see Figure 19). (A list of bond lengths and angles, as well as the fractional atomic coordinates are given in Appendix A.)

From the X-ray structure it can be seen that the carbonyl group lies over the benzene ring. Initially we proposed that this was due to a π-stacking effect, however after calculating the distance and angle of the carbonyl from the plane of the benzene ring (C_{15}-Ar = 3.42Å, O_2-Ar = 3.22Å and the angle between carbonyl plane and aromatic plane = 27.6°), using a least squares method, we found no positive evidence to prove that what we were witnessing was not purely due to crystal packing. (For details of the least squares calculation see Appendix A.)

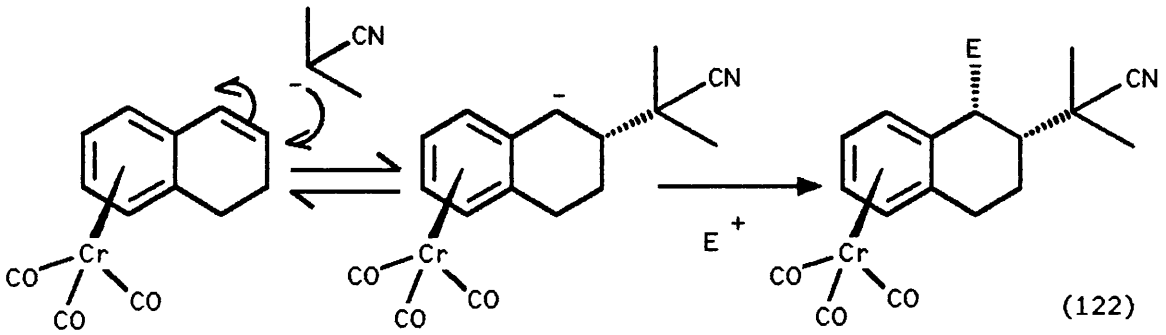
Figure 19


C18
C4
C6
C3
C5
C7
C2
C8
C10
C19
O1
C9
C1
F2
C11
C14
C12
F3
C16
C15
N1
C13
F1
O2
C17

2.2.6 The Chromium Complexation Reaction and Final Ring Closure

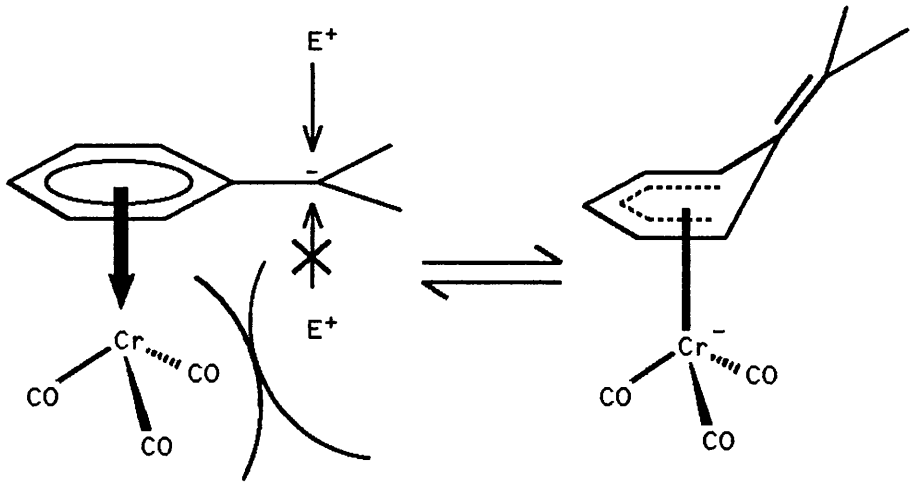
Initially, our intention was to make use of a reaction originally described by Knox *et al.*[47] and subsequently investigated by Semmelhack *et al.*[48] and Uemura *et al.*[49] (see Scheme 34), to complete the final ring closure in a stereoselective manner.

Scheme 34



This reaction makes use of the stabilizing effect of the chromium tricarbonyl unit upon benzylic anions[50] (see Figure 20), which is exerted as a result of its electron withdrawing properties. The chromium tricarbonyl unit also controls the directional approach of any electrophiles (E^+) because of its large steric bulk.[51]

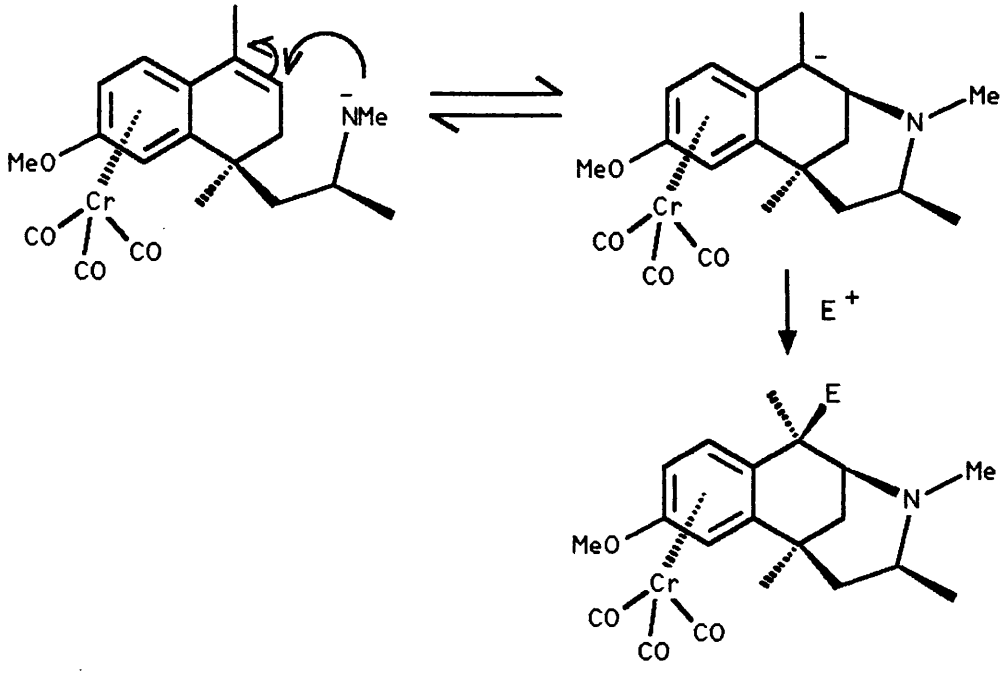
Figure 20



We proposed that after forming the chromium complex of the

dihydronaphthalenethanamine (123), it would then be possible to perform the ring closure reaction *via* the anion of the amino group. Chromium complexation should be selective to the least sterically hindered face,[61] again due to the size of the chromium tricarbonyl group. Any attacking electrophile would come from the face opposite the chromium tricarbonyl moiety, thus controlling the stereochemistry at C-1 of the benzomorphan (83).

Scheme 35



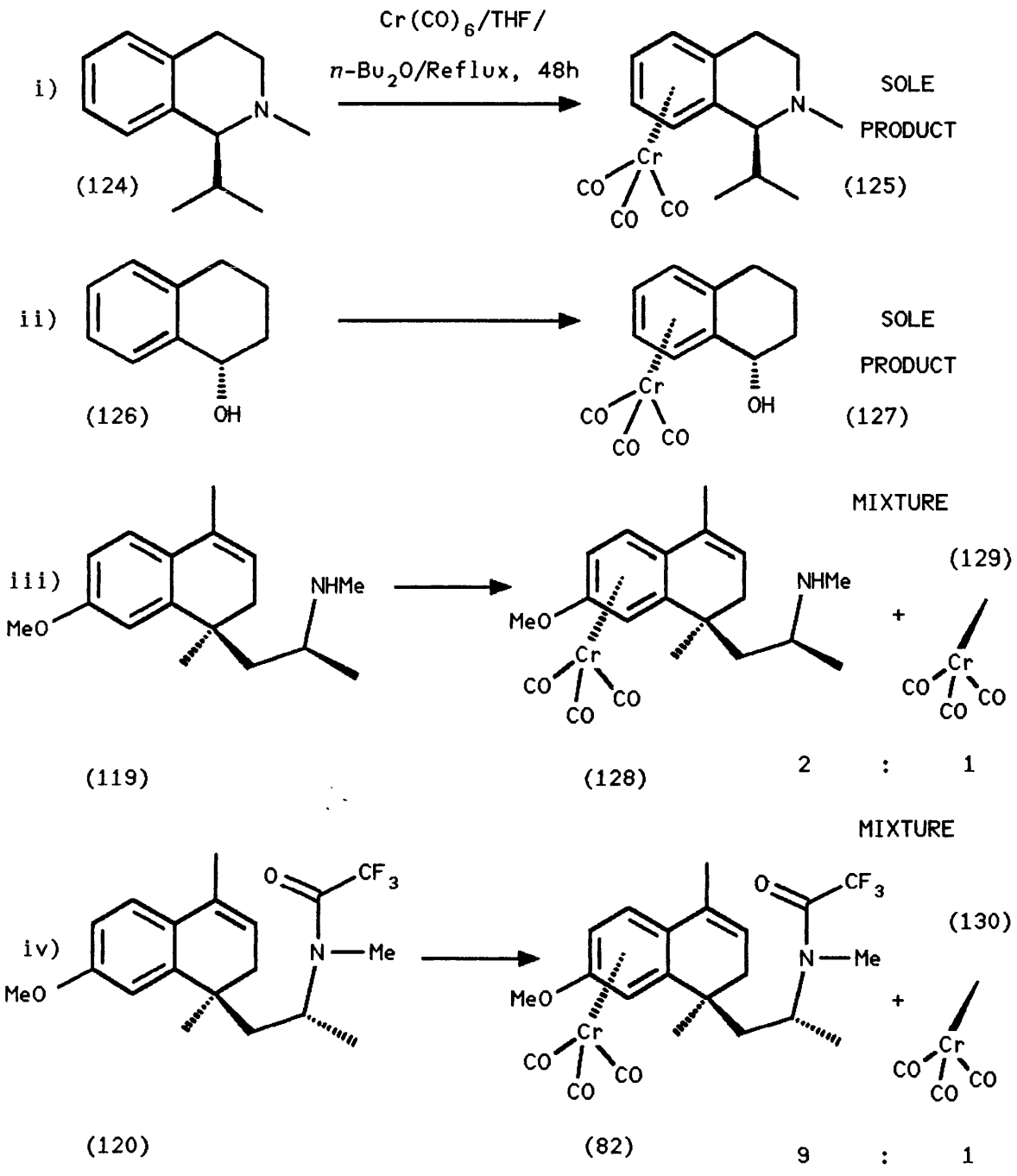
Usual conditions[52] were employed for the chromium complexation, which entailed heating chromium hexacarbonyl and the substrate, under reflux, in a solution of tetrahydrofuran/di-*n*-butyl ether (1:9), for 48 h. Complexation of the dihydronaphthalenethanamine (119) gave rise to an amount of black tar, as well as the required chromium tricarbonyl complex. The black tar is an indication that polymerisation is occurring. Polymerisation during complexation has long been known as a side reaction for styrenes and dihydronaphthalenes[53], and various methods have been used to avoid it.[54]

No such polymerisation was observed in the complexation of the trifluoroacetyl dihydronaphthalenethanamine (120), indicating that it was the presence of the unprotected amino group that was causing the problem, rather than polymerisation of the dihydronaphthalene moiety *per se*. (Polymerisation was not expected in this case due to the sterically hindered nature of the double bond.)

The dihydronaphthalenethanamine (119) gave rise to a 2:1 mixture of *trans*- to *cis*-chromium complexes as an orange oil in 24% yield. These two isomers were not separable by column chromatography and were extremely air and light sensitive. This result should be compared to the complexation of the trifluoroacetyl derivative (120), which gave the required product as a 9:1 mixture of *trans*- to *cis*-complexes. These two isomers were separated by column chromatography and isolated as orange solids in 36% and 4% yields respectively. (Starting material was also recovered in a 58% yield.)

Stereoselective control of chromium complexation has been demonstrated by Davies *et al.*[55] using the 1-isopropyltetrahydroisoquinoline (124) (see Scheme 36), where the sole product from the complexation is the *trans*-compound. It was also shown by Davies *et al.*[55] that for 1-hydroxytetrahydronaphthalene (126) only the *cis*-isomer is obtained upon complexation. (A mechanism involving initial chelation to an oxygen lone pair, followed by delivery to the proximate face has been cited for the latter reaction.[56]) This guiding effect may explain why the selectivity in the complexation reaction of the dihydronaphthalenethanamine (119) is only 2:1, since the steric and electronic factors are now competing with each other. The selectivity for the complexation of the trifluoroacetyl derivative (120),

Scheme 36



in which the lone pair is much less readily available, is 9:1 in favour of the *trans*-complex.

Measurement of the *cis*:*trans* ratio was determined by comparing the chemical shifts of the methyl groups at the 1'- and 2-positions, in the ^{1}H n.m.r. spectra. Examination of the ^{1}H n.m.r.

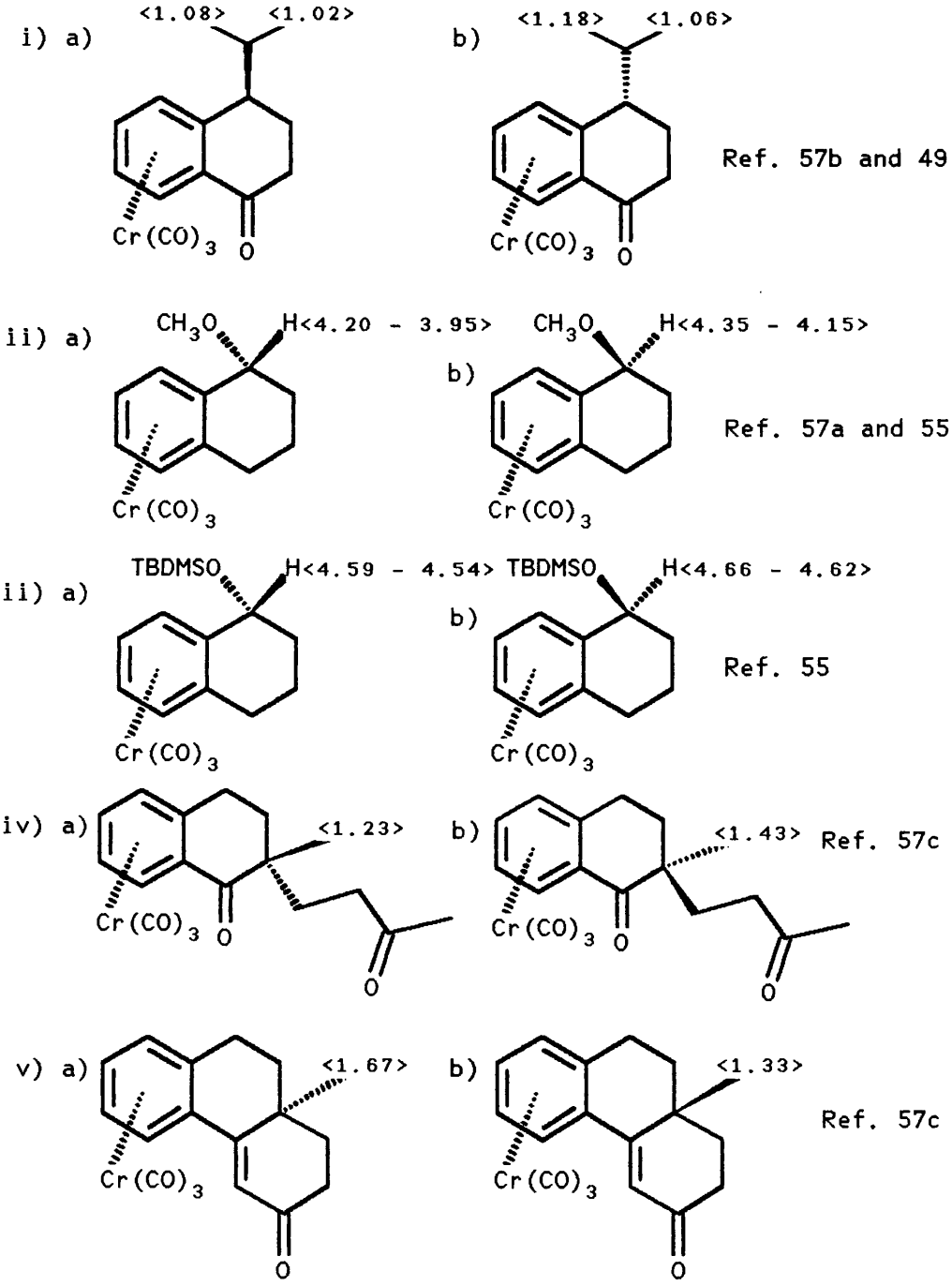
spectra of analogous compounds in the literature reveals that the chromium unit exerts a small deshielding effect on any groups situated on the same face of the molecule. This downfield shift in signals for groups on the same face as the chromium moiety is only visible when the *cis*- and *trans*-complexes are compared (see Figure 21).

Of the seven applicable examples found,[49,55,57] all exhibited this deshielding effect. The configuration of these structures were determined by X-ray crystallography or were based on the fact that the chromium group had been used to control stereochemistry in their synthesis.[57c]

The ^1H n.m.r. spectrum of the dihydronaphthalenethanamine chromium tricarbonyl complex (123) clearly showed the upfield shift in the aromatic protons caused by the chromium atom, where the signals for the resonances of these three protons were now occurring at δ 5.69–5.12 ppm (normally these protons resonate at δ 7.21–6.69 ppm), together with the signal for the alkenic H-3' proton. As in all the ^1H n.m.r. spectra of the chromium complexes taken, the signals were broadened by the presence of small amounts of paramagnetic chromium(III) species, which occur as impurities; this made precise assignment impossible. It was however, possible to assign the major peaks observed. The chemical shifts of the resonances for the N-CH_3, 1'-CH_3 and H-3 methyl groups for both the isomers are listed in Table 1.

From this table it can be seen that the resonance of the methyl group H-3 occurs at a lower field for the minor isomer, whereas the resonance for the methyl group 1'-CH_3 occurs at lower field for the major isomer. These observations, if taken in the context of the trend

Figure 21



() = chemical shift, δ ppm

shown in Figure 21, suggest that the major isomer is the *trans*-complex, while the minor isomer is the *cis*-complex.

In the case of the trifluoroacetyl derivative, the *cis*- and *trans*-complexes, (130) and (82), were separable by column

Figure 22

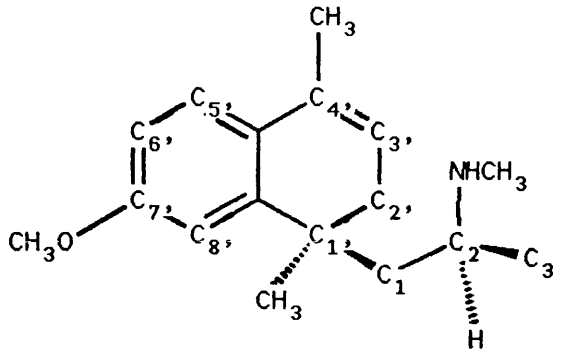


Table 1

SIGNAL	CHEMICAL SHIFT (δ) ppm	
	MAJOR ISOMER	MINOR ISOMER
N-CH_3	2.28	2.17
1′-CH_3	1.47	1.16
H-3	0.72	0.90

chromatography and the stereochemistry of chromium in the *trans*-complex was apparent by virtue of the stereochemistry of the final product, as well as from the evidence of the ^1H n.m.r. spectra (see Table 2).

Table 2

SIGNAL	CHEMICAL SHIFT (δ) ppm	
	TRANS	CIS
N-CH_3	2.63	3.05
1′-CH_3	1.44	1.12
H-3	1.08	1.31

Assignment of the ^1H n.m.r. spectrum of the *trans*-complex (82)

was based on irradiation studies and also by comparison to the spectrum of the uncomplexed trifluoroacetyldihydronaphthalen-ethanamine (120). This clearly shows the alkenic resonance for H-3' at δ 5.66 ppm as a doublet, J = 6 Hz, lower field than the aromatic protons, the signals of which lie at δ 5.58 and 5.17 ppm. The alkenic resonance is coupled to the signal for one of the H-2' protons, a doublet of doublets, J = 7 and 17 Hz, at δ 2.09 ppm. Of the aromatic protons it is the H-5' proton resonance which appears lowest field at δ 5.58 ppm and is recognizable as a doublet with a coupling constant of J = 7 Hz. The signal at δ 5.17 ppm is a multiplet combining the resonances of both the H-6' and H-7' protons.

The cyclisation reaction was attempted on both the amino (123) and trifluoroacetamido (82) complexes. *t*-Butyl lithium was added to a solution of the amino derivative at 0°C, to deprotonate the amine function. Ammonium chloride solution was then added at -78°C to quench the reaction. After the reaction had been allowed to warm to room temperature, it was worked up to afford only starting material. A bulky base was used to deprotonate the amine in order to try to reduce the chance of the base directly attacking the double bond.

For the trifluoroacetamido complex (82), methyl lithium was added at -78°C, with the intention that it would preferentially attack the carbonyl group of the trifluoroacetamide to form a tetrahedral intermediate, which would collapse to give the nitrogen anion and trifluoromethyl methyl ketone. A solution of dimethyl disulphide was then added at -78°C, to trap any ring closed anion that had formed. The only compounds isolated from this reaction were starting material, the amino complex (123) and a small amount of the acetamido complex (131). The presence of the acetamido product indicates that the

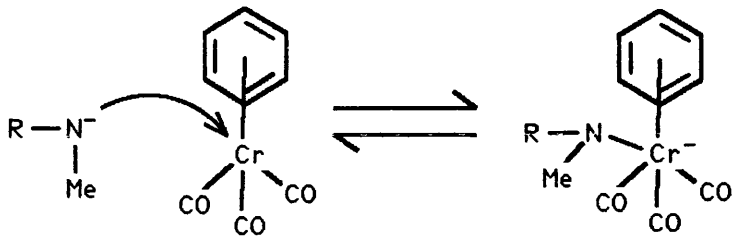
tetrahedral intermediate is also collapsing to give a trifluoromethyl anion, to a smaller extent.

Alkylation of a dihydronaphthalene chromium tricarbonyl complex has been described by Semmelhack *et al.*,[48] using a stabilised anion (see Scheme 34). When the reaction was quenched with ammonium chloride solution at temperatures between -78°C and 25°C, only the addition product (122, E = H) was observed. However, when methyl iodide was used to quench the reaction, a mixture of starting material, the addition product (122, E = H) and the required addition product (122, E = Me) were obtained. Quenching at 25°C gave only starting material, while quenching at -78°C gave a 1:2:6 mixture of starting material, the protonated addition product (122, E = H) and the methylated addition product (122, E = Me). When the reaction was quenched at 0°C, a 4:1 mixture of the protonated and methylated products was obtained. Semmelhack proposed that the initial attack by the lithium dimethylacetonitrile was an equilibrium process. The equilibrium was assumed to lie well over towards the side of addition product anion. At higher temperatures the equilibrium was rapid enough to produce a sufficient concentration of the dimethyl-acetonitrile anion to allow the methyl iodide to react selectively with it.

Initially we thought that the failure of our ring closure reaction was due to this type of equilibration, which was heavily in favour of the ring opened anion (see Scheme 35). In order to try and selectively quench the ring closed form, dimethyl disulphide was used to quench the reaction. It was proposed that weak nature of the sulphur-nitrogen bond would preclude the quenching of the nitrogen anion before ring closure was achieved. Unfortunately, this attempt

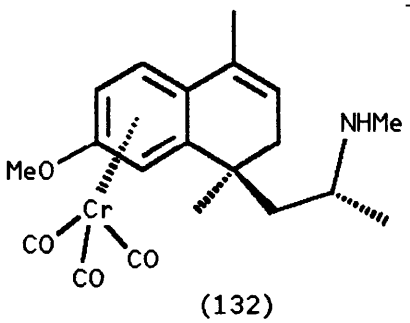
also proved unsuccessful. One explanation may be that the anion of the amino group is complexing to the chromium in an intermolecular fashion, thus preventing further reaction (see Figure 23).

Figure 23

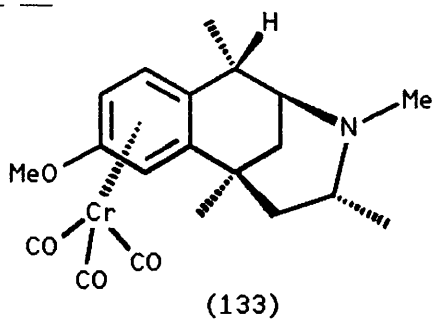


To circumvent this problem, the ring closure reaction was attempted using potassium carbonate in aqueous methanol as the base, and treating the resultant mixture with ultrasound. Using potassium carbonate avoids any chance of the reverse reaction occurring, because any ring closed intermediate formed immediately picks up a proton. The conditions used had previously been applied to the uncomplexed trifluoroacetyl dihydronaphthalenethanamine (120) to hydrolyse the trifluoroacetyl group and had given the deprotected amine (132) in quantitative yield. When repeated on the trifluoroacetyl

Figure 24



(132)



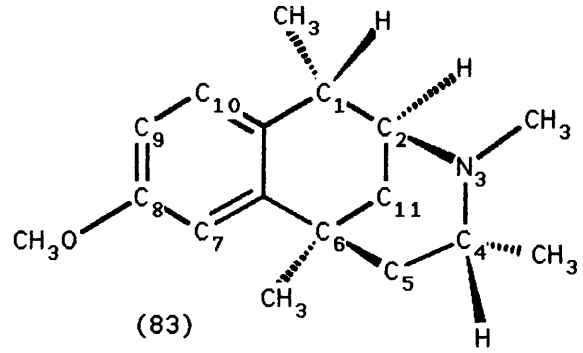
(133)

dihydronaphthalenethanamine chromium complex (82), as well as hydrolysing the trifluoroacetyl group, the conditions slowly gave rise to the ring closed product (133). After 72 h, the ring closed product was isolated, decomplexed and purified by preparative thin-layer

chromatography to give the hexahydro-2,6-methano-3-benzazocine (83) in 40% yield (based on recovered starting material).

Decomplexation was performed by dissolving the complex in ether and standing the solution in a sunny position, in the presence of air, for 24 h.

Figure 25



(83)

The ^{1}H n.m.r. spectrum of the hexahydro-2,6-methano-3-benzazocine (83) was assigned with the help of a two dimensional COSY-90 experiment. The resonance of the proton H-1 at δ 3.12 ppm is seen as a broad quartet, J = 7.1 Hz, and is only coupled to the signal for the 1-CH_3 group, which occurs as a doublet, J = 7.1 Hz, at δ 1.22 ppm. No coupling is observed with H-2, which corresponds to a dihedral angle of 80-90° (according to the Karplus equation), revealing that the methyl group at C-1 is in the α-configuration.[58] The proton resonance of H-2 is visible as a broad triplet, J = 3.1 Hz, at δ 2.88 ppm and is coupled to the signals for the H-11 protons at δ 1.97 and 1.69 ppm. These are observed as a doublet of triplets, J = 2.6 and 12.6 Hz, and a doublet of doublet of doublets, J = 1.1, 3.8 and 12.6 Hz, respectively. (The further splitting present in these signals is probably due to a long range W-effect.) The resonance of H-4 occurs as a multiplet at δ 2.07 ppm and is coupled to the signal for the methyl group, 4-CH_3, a doublet, J = 6.2 Hz, at δ 0.92 ppm, and the

resonance for the two protons, H-5, which is obscured by the signal for the methyl group, 6-CH_3, at δ 1.35 ppm. The methyl group, 4-CH_3, is confirmed as being in the α-position by its chemical shift. If it was in the β-position it would be expected to occur at higher field (δ 0.4-0.5 ppm)[59] due to the shielding effect of the aromatic ring over which the methyl group would be positioned.

The ^{13}C n.m.r. spectrum shows signals for all the resonances of the required carbon atoms; however two of these signals are coincident. These are the signals relating to either C-2 or C-4, and C-5, which show up as single peak at δ 50.1 ppm. In the DEPT 90 spectrum this signal is observed as a positive peak and in the DEPT 135 spectrum it is seen as a negative peak. An off resonance ^{13}C n.m.r. spectrum confirmed this conclusion, showing the signal at δ 50.1 ppm as an overlapping doublet and triplet.

Mass spectroscopy revealed the mass ion, *m/z* 259 (M^+, 20%), and the fragment ion, *m/z* 244 (100, $M-CH_3$).

Optical rotation studies showed that the compound was laevorotatory, thus confirming the absolute configuration of the compound.[60] Enantiomeric excess was determined to be 86% by ^1H n.m.r. using the chiral solvating reagent TFAE.

EXPERIMENTAL

EXPERIMENTAL

GENERAL

Chemicals, solvents and reagents were purified and dried, where appropriate, before use by standard methods. Preparative column chromatography[68] was normally carried out on silica gel 60 GF7736 or 9385 (E. Merck), or on alumina (Camag, Fisons 100-250 mesh). Thin-layer chromatography (t.l.c.) was carried out routinely on silica gel 60 GF254 (E. Merck). Proton (^{1}H n.m.r.) and Carbon-13 (^{13}C n.m.r.) nuclear magnetic resonance spectra were recorded at 270 MHz and 68 MHz respectively, in deuteriated chloroform solution, unless stated otherwise, on a JEOL FX270 instrument. Chemical shifts are expressed in p.p.m. (δ) downfield from tetramethylsilane (TMS) as standard and coupling constants (J) in Hertz (Hz). Ultra-violet/visible spectra (U.V.) were recorded for 95% ethanolic solutions on a Perkin-Elmer Lambda-3 spectrophotometer. Infrared (I.R.) spectra were measured on a Perkin-Elmer 1310 instrument. Mass spectra (M.S.) were recorded on an A.E.I. MS12 mass spectrometer using E.I. at 70 eV unless otherwise stated. Mass to charge ratios are quoted and their relative intensity (%) are enclosed in parentheses. Normally, where solvents had to be removed, a rotary evaporator operating at water-pump pressure was employed. (Exceptions to this routine are noted.) Where solutions were degassed, the freeze-pump-thaw method was used. When ether is mentioned, it is always diethyl ether that it refers to. Enantiomeric excess was determined by ^{1}H n.m.r. using the chiral solvating agent (-)-1-(9-anthryl)-2,2,2-trifluoroethanol (TFAE) to resolve the signals.

Ethyl 2-(3-methoxyphenyl)-2-methyl-1-oxiranecarboxylate (85)

Sodium (46 g, 2.0 mol) was added portionwise to absolute ethanol (750 cm^3) being stirred at 0°C under a nitrogen atmosphere over a period of 4 h. The mixture was stirred at room temperature for 12 h, to ensure that all the sodium had dissolved, before being cooled to 0°C again. A mixture of 3'-methoxyacetophenone (150.2 g, 1.0 mol) and ethyl chloroacetate (245.1 g, 2.0 mol) in benzene (250 cm^3) was added at 0°C over a period of 1 h. The resultant mixture was stirred at 0°C for 1 h and at room temperature for a further 3 h. The reaction mixture was quenched by adding it to a slurry of ice (1000 g) and glacial acetic acid (100 cm^3) and then extracted with dichloromethane (4x500 cm^3). The organic portions were combined, washed with saturated aqueous sodium bicarbonate solution (200 cm^3), and then with saturated brine (100 cm^3). The dried (Na_2SO_4) organic layer was evaporated under reduced pressure to give an orange oil. Distillation gave the title compound as a yellow oil (223.1 g, 94%). b.p. 140-145°C at 0.1 mmHg. IR(neat) ν_{max} 2980, 2920sh, 2820, 1730 (CO), 1600sh, 1580, 1450, 1430, 1290, 1220, 1080, 1040, 860, 830, 790, 750 and 700 cm^{-1}; ^1H n.m.r. ($CDCl_3$) δ_H (Isomer I) 7.20 (1 H, t, *J* 7.9 Hz, 5'-H), 6.94-6.88 (1 H, m, 6'-H), 6.85 (1 H, t, *J* 2.6 Hz, 2'-H), 6.77 (1 H, ddd, *J* 7.9, 2.6 and 0.9 Hz, 4'-H), 4.24 (2 H, ABX_3, J_{AB} 10.8 Hz, J_{AX} 7.3 Hz, J_{BX} 7.2 Hz, $OC\underline{H}_2CH_3$), 3.76 (3 H, s, $OC\underline{H}_3$), 3.34 (1 H, s, 1-H), 1.72 (3 H, s, 2-$C\underline{H}_3$) and 1.31 (3 H, t, *J* 7.1 Hz, $OCH_2C\underline{H}_3$),δ_H (Isomer II) 7.18 (1 H, t, *J* 8.2 Hz, 5'-H), 6.94-6.90 (2 H, m, 2'- and 6'-H), 6.76 (1 H, ddd, *J* 8.2, 2.6 and 1.1 Hz, 4'-H), 3.90 (2 H, ABX_3, J_{AB} 14.3 Hz, $J_{AX,BX}$ 7.1 Hz, $OC\underline{H}_2CH_3$), 3.78 (3 H, s, $OC\underline{H}_3$), 3.59 (1 H, s, 1-H), 1.72 (3 H, s, 2-$C\underline{H}_3$) and 0.92 (3 H, t, *J* 7.1 Hz, $OCH_2C\underline{H}_3$); ^{13}C n.m.r.

($CDCl_3$) δ_C (Isomer I) 166.8 (CO), 159.6 (3'-C), 141.7 (1'-C), 129.2, 117.3, 113.3 and 110.4 (4xAr-CH), 61.3 (2-C), 60.9 (1-C), 60.9 (OCH_2CH_3), 54.7 (OCH_3), 16.7 and 14.0 ($2xCH_3$),δ_C (Isomer II) 166.6 (CO), 159.1 (3'-C), 138.6 (1'-C), 128.8, 118.5, 113.7 and 111.5 (4xAr-CH), 63.4 (2-C), 60.5 (OCH_2CH_3), 60.4 (1-C), 54.9 (OCH_3), 24.4 and 13.7 ($2xCH_3$); MS(m/z) 236 (*M*+, 31%), 190 (8), 163 (100) and 162 (100).

Ethyl 2-hydroxy-3-(3-methoxyphenyl)-3-butenoate (86)

Concentrated sulphuric acid (3 cm^3) was added dropwise to a stirred solution of the oxirane ester (85) (115 g, 0.49 mol) in ether (500 cm^3) at 0°C. The solution was stirred at room temperature for 30 min and then was washed with water (50 cm^3), then saturated aqueous sodium bicarbonate solution (2x100 cm^3), and finally saturated brine (50 cm^3). The solution was dried (Na_2SO_4) and evaporated to give the title compound as an orange oil (95.9 g, 83%). b.p. 127-130°C at 0.1 mmHg. IR(neat) ν_{max} 3500 (OH), 3000, 2950, 2850, 1740 (CO), 1600, 1580, 1490, 1470, 1430, 1290, 1220, 1090, 1050, 920, 860 and 780 cm^{-1}; ^1H n.m.r. ($CDCl_3$) δ_H 7.23 (1 H, t, *J* 8.0 Hz, 5'-H), 7.01-6.95 (2 H, m, 6'- and 2'-H), 6.84 (1 H, ddd, *J* 8.0, 2.5 and 0.9 Hz, 4'-H), 5.49 (1 H, s, 4-H), 5.44 (1 H, s, 4-H), 5.02 (1 H, s, 2-H), 4.26-4.06 (2 H, m, ABX_3 J_{AB} 10.7 Hz and $J_{AX,BX}$ 7.1 Hz, OCH_2CH_3), 3.79 (3 H, s, OCH_3) 3.44 (1 H, br s, OH) and 1.12 (3 H, t, *J* 7.1 Hz, OCH_2CH_3); ^{13}C n.m.r. ($CDCl_3$) δ_C 173.3 (CO), 159.3 (3'-C), 145.8 and 139.9 (1'-C and 3-C), 129.2 (Ar-CH), 119.3 (Ar-CH), 117.2 (4-C), 113.3 (Ar-CH), 112.6 (Ar-CH), 73.6 (2-C), 62.0 (OCH_2CH_3), 55.1 (OCH_3) and 13.8 (OCH_2CH_3); MS(m/z) 236 (*M*+, 43%), 163 (100, *M*-COOEt), 150 (25) and 135 (73); Analysis (Found: C, 65.9; H, 6.84, $C_{13}H_{16}O_4$ requires: C, 66.1; H, 6.84%).

2-Hydroxy-3-(3-methoxyphenyl)-3-butenoic acid (87)

A mixture of the butenoate ester (86) (95.9 g, 0.41 mol) and 2 M aqueous sodium hydroxide solution (500 cm^3), was stirred at room temperature for 12 h. The orange solution formed was extracted with dichloromethane (100 cm^3) and the aqueous layer acidified to pH 2 with concentrated hydrochloric acid. The aqueous layer was then extracted with dichloromethane (4x300 cm^3), and the organic washings from the acid layer combined. This organic portion was washed with saturated brine (50 cm^3), dried (Na_2SO_4) and evaporated under reduced pressure to give the title compound as a yellow waxy solid (81.3 g, 96%). IR(neat) ν_{max} 3400-2900br (acid OH), 1700 (CO), 1590 sh, 1570, 1480, 1280, 1210, 1100, 1070, 1040, 910, 870, 780 and 680 cm^{-1}; ^1H n.m.r. ($CDCl_3$) δ_H 8.0-6.6 (2 H, br s, CHO<u>H</u> and COO<u>H</u>), 7.19 (1 H, t, *J* 7.9 Hz, 5'-H), 6.99-6.94 (2 H, m, 2'- and 6'-H), 6.81 (1 H, dd, *J* 7.9 and 2.0 Hz, 4'-H), 5.49 (1 H, s, 4-H), 5.41 (1 H, s, 4-H), 5.07 (1 H, s, 2-H) and 3.81 (3 H, s, OC<u>H</u>$_3$); ^{13}C n.m.r. ($CDCl_3$) δ_C 176.5 (CO), 159.2 (3'-C), 144.9 and 139.4 (1'-C and 3-C), 129.3 (Ar-<u>C</u>H), 119.3 (Ar-<u>C</u>H), 117.7 (4-C), 113.4 (Ar-<u>C</u>H), 112.6 (Ar-<u>C</u>H), 73.2 (2-C) and 55.1 (O<u>C</u>H$_3$); MS(m/z) 208 (*M*$^+$, 25%), 163 (25, *M*-COOH) and 135 (55); Acc. MS(m/z), (Found: 208.0733 (*M*$^+$, 98%), $C_{11}H_{12}O_4$ requires: 208.0734, -0.5 ppm).

2-(3-Methoxyphenyl)propanal (88)

A mixture of the butenoic acid (87) (81.2 g, 0.49 mol) and 3 M hydrochloric acid (250 cm^3) was placed in a two necked round bottomed flask (500 cm^3) fitted with an inlet tube connected to a steam generator and a splash head fitted with a water condenser. The contents of the flask was then steam distilled until no further product was visible by tlc in the distillate. The aqueous distillate was

extracted with dichloromethane (3x1000 cm^3) and the combined organic portions were washed with saturated aqueous sodium bicarbonate solution (250 cm^3), dried (Na_2SO_4) and evaporated under reduced pressure to give a colourless oil (36.3 g). Distillation gave the title compound as a colourless oil (32.2 g, 40%). b.p. 122-123°C at 8 mmHg. IR(neat) ν_{max} 2960, 2920, 2820, 2700, 1710 (CHO), 1590, 1580, 1480, 1450, 1260, 1150, 1030, 900, 780 and 690 cm^{-1}; ^1H n.m.r. ($CDCl_3$) δ_H 9.67 (1 H, d, *J* 1.3 Hz, C<u>H</u>O), 7.30 (1 H, t, *J* 7.9 Hz, 5'-H), 6.86-6.78 (2 H, m, 4'- and 6'-H), 6.76 (1 H, t, *J* 2.0 Hz, 2'-H), 3.81 (3 H, s, OC<u>H</u>$_3$), 3.60 (1 H, qd, *J* 7.0 and 1.3 Hz, 2-H) and 1.43 (3 H, d, *J* 7.0 Hz, 3-H); ^{13}C n.m.r. ($CDCl_3$) δ_C 200.8 (<u>C</u>HO), 160.1 (3'-C), 139.2 (1'-C), 130.0 (Ar-<u>C</u>H), 120.5 (Ar-<u>C</u>H), 114.0 (Ar-<u>C</u>H), 112.6 (Ar-<u>C</u>H), 55.1 (O<u>C</u>H$_3$), 52.9 (2-C) and 14.4 (3-C); MS(E.I., low eV, m/z), 164 (*M*$^+$, 83%), 150 (18, *M*-CH_2) and 135 (100, *M*-CHO); Acc. MS(m/z) (Found: 164.0831 (*M*$^+$, 33%), Calc. for $C_{10}H_{12}O_2$: 164.0837, -3.7 ppm).

2-(3-Methoxyphenyl)propanal (88)

Dry tetrahydrofuran (75 cm^3) was added in one portion to a mixture of methoxymethyltriphenylphosphonium chloride (18.8 g, 54 mmol) and potassium *t*-butoxide (8.0 g, 54 mmol) and the mixture stirred at room temperature for 45 min, under a nitrogen atmosphere. 3'-Methoxyacetophenone (3.3 cm^3, 3.7 g, 25 mmol) was added dropwise over a period of 15 min to the deep red solution of the ylid, and the solution was then stirred for a further 1 h at room temperature. The solution was poured onto ice (200 g) and extracted with ether (3x50 cm^3). The combined extracts were washed with brine (20 cm^3), dried ($MgSO_4$) and evaporated under reduced pressure to give a yellow oil. Purification of the intermediate enol ether by "suction flash" column

chromatography on silica gel, eluting with ethyl acetate/60-80°C petroleum ether (using a gradient from 1:49 to 1:1) gave no separation due to the triphenylphosphine oxide by-product, which co-ran with the product. Perchloric acid (60-64%, 20 cm^3) was added to a solution of the residue in ether (50 cm^3), which was then stirred at room temperature for 16 h, under a nitrogen atmosphere. The solution was poured onto ice (100 g) and the mixture was extracted with ethyl acetate (3x50 cm^3). The combined extracts were washed with a saturated aqueous sodium bicarbonate solution (50 cm^3), saturated brine (30 cm^3), dried ($MgSO_4$) and evaporated under reduced pressure to give a brown oil. Removal of the triphenylphosphine oxide by trituration with 60-80°C petroleum ether proved impossible. Purification by "suction flash" column chromatography on silica gel, eluting initially with 60-80°C petroleum ether and then a gradient mixture of ether/60-80°C petroleum ether (1:19 to 1:9 to 3:17) removed all traces of the triphenylphosphine oxide. Further purification by "suction flash" column chromatography on silica gel, eluting with ether/60-80°C petroleum ether (1:19), gave the title compound as a colourless oil (1.1 g, 27%). The spectral details were identical with those described previously for this compound (see p.66).

1-(3-Methoxyphenyl)-1-methyloxirane (92)

Sodium hydride (60% dispersion in mineral oil, 1.51 g, 37.8 mmol), which had been washed with dry 40-60°C petroleum ether (3x30 cm^3), and trimethyl sulphonium iodide (8.8 g, 40 mmol) were placed in a dry, three necked, round bottomed flask (250 cm^3) fitted with an overhead stirrer and a vacuum/nitrogen line. The flask was evacuated and then filled with nitrogen and this process was repeated twice.

Dry dimethyl sulphoxide (40 cm^3) was added slowly and the suspension stirred gently until hydrogen production had ceased. A solution of 3'-methoxyacetophenone (5.0 g, 33.3 mmol) in dry dimethyl sulphoxide (15 cm^3) was added to the stirred suspension at room temperature, and the reaction mixture was then heated at 50°C for 2 h. After cooling, the reaction mixture was poured onto ice (80 g) and extracted with ether (3x60 cm^3). The combined organic extracts were washed with water (20 cm^3), dried (Na_2SO_4), and evaporated under reduced pressure to give a yellow oil. Purification by "suction flash" column chromatography on silica gel, eluting with ethyl acetate/60-80°C petroleum ether (1:9), gave the title compound as a colourless oil (3.0 g, 52%). IR(neat) ν_{max} 3040, 2960, 2920, 2830, 1600sh, 1580, 1480, 1450, 1420, 1290, 1220, 1045, 880, 830, 780 and 695 cm^{-1}; ^1H n.m.r. ($CDCl_3$) δ_H 7.24(1 H, t, *J* 8.0 Hz, 5'-H), 6.95 (1 H, ddd, *J* 8.0, 2.6 and 1.0 Hz, 6'-H), 6.91 (1 H, m, 2'-H), 6.80 (1 H, ddd, *J* 8.0, 2.6 and 1.0 Hz, 4'-H), 3.78 (3 H, s, $OC\underline{H}_3$), 2.94 (1 H, d, *J* 5.5 Hz, *E*-2-H), 2.76 (1 H, dd, *J* 5.5 and 0.7 Hz,*Z*-2-H) and 1.69 (3 H, d, *J* 0.7 Hz, 1-$C\underline{H}_3$); ^{13}C n.m.r. ($CDCl_3$) δ_C 159.6 (3'-C), 142.8 (1'-C), 129.3 (Ar-$\underline{C}$H), 117.7 (Ar-$\underline{C}$H), 112.9 (Ar-$\underline{C}$H), 110.7 (Ar-$\underline{C}$H), 56.8 (2-C), 56.6 (1-C), 55.1 ($O\underline{C}H_3$) and 21.7 (1-$\underline{C}H_3$); MS(m/z) 164 (*M*+, 91%), 163 (94, *M*-H), 149 (41), 135 (48), 133 (86), 121 (50) and 91 (100); Analysis (Found: C, 72.7; H, 7.33, $C_{10}H_{12}O_2$ requires: C, 73.1; H, 7.37%).

2-(3-Methoxyphenyl)propanal (88)

Boron trifluoride-etherate (1 cm^3) was added dropwise to a stirred solution of the oxirane (92) in dry ether, at 0°C. The reaction was stirred at room temperature for 15 min and then ether (100 cm^3) was added. The solution was washed with saturated aqueous sodium

bicarbonate solution (2x30 cm^3), dried (Na_2SO_4) and evaporated under reduced pressure to give a yellow oil (2.9 g). Purification by "flash" column chromatography on silica gel, eluting with ethyl acetate/60-80°C petroleum ether (1:9) gave the title compound as a colourless oil (1.9 g, 63.3%). The spectral details were identical with those described previously for this compound (see p.66).

4-(3-Methoxyphenyl)-4-methyl-2-cyclohexen-1-one (89)

A 40% methanolic solution of benzyltrimethylammonium hydroxide (26.6 cm^3, 24.5 g, 59 mmol) was added over 1 h to a stirred solution of the aldehyde (88) (32.2 g, 196 mmol) and methyl vinyl ketone (18.0 cm^3, 15.1 g, 216 mmol) in *t*-butanol (150 cm^3) at 0°C under a nitrogen atmosphere. The reaction was stirred at room temperature for 2 h, then quenched on ice (300 g), and extracted with ether (3x300 cm^3). The organic portions were combined, washed with saturated brine (50 cm^3), dried (Na_2SO_4) and evaporated under reduced pressure to give a pale yellow oil. Distillation gave the title compound as a colourless oil (30.0 g, 71%). b.p. 124-131°C at 0.05 mmHg. IR(neat) ν_{max} 2950, 2860sh, 2820, 1670 (α,β-unsaturated CO), 1590, 1570, 1480, 1450, 1420, 1280, 1250, 1220, 1200, 1050, 830, 780 and 700 cm^{-1}; ^1H n.m.r. ($CDCl_3$) δ_H 7.27 (1 H, t, *J* 8.2 Hz, 5'-H), 6.93-6.87 (3 H, m, 2-H, 2'-H and 6'-H), 6.79 (1 H, dd, *J* 8.2 and 2.5 Hz, 4'-H), 6.11 (1 H, d, *J* 10.1 Hz, 3-H), 3.80 (3 H, s, $OC\underline{H}_3$), 2.45-2.05 (4 H, m, 5- and 6-H) and 1.54 (3 H, s, 4-$C\underline{H}_3$); ^{13}C n.m.r. ($CDCl_3$) δ_C 199.4 (CO), 159.7 (3'-C), 156.9 (2-C), 146.9 (1'-C), 129.6, 128.5, 118.6, 112.9 and 111.2 (4xAr-$\underline{C}H$ and 3-C), 55.2 ($O\underline{C}H_3$), 40.6 (4-C), 37.9 (6-C), 34.6 (5-C) and 27.6 (4-$\underline{C}H_3$); MS(m/z) 216 (*M*+, 100%), 201 (29, *M*-CH_3), 188 (35), 174 (32), 173 (37) and 158 (50); Acc. MS(m/z) (Found: 216.1141 (*M*+,

100%), $C_{14}H_{16}O_2$ requires: 216.1148, -3.2 ppm).

4-(3-Methoxyphenyl)-4-methylcyclohexanone (76)

A solution of the cyclohexenone (89) (20.0 g, 92.4 mmol) in glacial acetic acid (200 cm^3) was hydrogenated in the presence of 10% palladium on charcoal catalyst (1.0 g), at atmospheric pressure, until hydrogen uptake ceased. The reaction mixture was filtered through a bed of Celite to remove the catalyst, and the filter bed washed with ethyl acetate (4x100 cm^3). Water (500 cm^3) was added to the combined filtrates and the organic layer separated. The aqueous layer was extracted with ethyl acetate (3x100 cm^3). All the organic layers were combined, washed with water (100 cm^3), saturated brine (50 cm^3), dried (Na_2SO_4) and evaporated under reduced pressure to give a colourless oil. Crystallization from 60-80°C petroleum ether gave the title compound as colourless needles or plates (18.3 g, 91%). m.p. 66.5-67.5°C. IR(neat) ν_{max} 2950, 2860sh, 1710 (CO), 1590sh, 1570, 1480sh, 1450, 1420, 1280, 1220, 1050, 870, 780 and 700 cm^{-1}; ^1H n.m.r. ($CDCl_3$) δ_H 7.31 (1 H, t, *J* 8.0 Hz, 5'-H), 7.03 (1 H, ddd, *J* 8.0, 2.1 and 0.9 Hz, 6'-H), 6.99 (1 H, t, *J* 2.1 Hz, 2'-H), 6.79 (1 H, ddd, *J* 8.0, 2.1 and 0.9 Hz, 4'-H), 3.83 (3 H, s, $OC\underline{H}_3$), 2.55-1.85 (8 H, m, $4xC\underline{H}_2$) and 1.31 (3 H, 4-$C\underline{H}_3$); ^{13}C n.m.r. ($CDCl_3$) δ_C 211.5 (CO), 159.8 (3'-C), 147.6 (1'-C), 129.6 (Ar-$\underline{C}H$), 117.9 (Ar-$\underline{C}H$), 112.5 (Ar-$\underline{C}H$), 110.2 (Ar-$\underline{C}H$), 55.0 ($O\underline{C}H_3$), 37.7 (4-C), 38.2 (2- and 6-C), 37.0 (3- and 5-C) and 31.0 (4-$\underline{C}H_3$); MS(m/z) 218 (M^+, 73%), 203 (8), 189 (12), 161 (73) and 148 (100); Analysis (Found: C, 76.8; H, 8.45, $C_{14}H_{18}O_2$ requires: C, 77.0; H, 8.33%).

(2S)-2-Methoxymethyl-N-[4-(3-methoxyphenyl)-4-methylcyclohexylidene]-1-pyrrolidinamine (93)

A mixture of (*S*)-1-amino-2-methoxymethylpyrrolidine (10 g, 77 mmol) and the cyclohexanone (76) (16 g, 73 mmol) was heated at 60°C for 18 h, with stirring, under an argon atmosphere. The reaction mixture was allowed to cool and then dissolved in ether (200 cm^3). This solution was washed with water (30 cm^3), saturated brine (10 cm^3), dried (Na_2SO_4) and evaporated under reduced pressure to give a yellow oil. Distillation gave the title compound as a colourless oil (21.8 g, 90%). b.p.176-178°C at 0.05 mmHg. $[\alpha]_D^{18°C}$ +175.3° (c 0.5 in $CHCl_3$); IR(0.5% in $CHBr_3$) ν_{max} 2920, 2870sh, 2830, 1640w (CN), 1610, 1580, 1490, 1460, 1430, 1240, 1050 and 780 cm^{-1}; ^1H n.m.r. ($CDCl_3$) δ_H (mixture of diastereomers -all signals doubled) 7.28 (1 H, 2xt, *J* 8.0 Hz, 5''-H), 7.03-6.94 (2 H, m, 2''- and 6''-H), 6.79-6.73 (1 H, m, 4''-H), 3.82 and 3.81 (3 H, 2xs, Ar-OC$\underline{H}_3$, 3.48-2.90 (5 H, m, 2-C$\underline{H}_2$, 2-H and 5-H), 3.37 and 2.20 (3 H, 2xs, $CH_2OC\underline{H}_3$), 2.58-1.59 (12 H, m, 6xC$\underline{H}_2$), 1.30 and 1.22 (3 H, 2xs, 4'-C$\underline{H}_3$); ^{13}C n.m.r. ($CDCl_3$) δ_C 169.1 and 168.3 (CN), 159.9 and 159.7 (3''-C), 150.1 and 148.5 (1''-C), 129.5 and 129.3 (Ar-$\underline{C}$H), 118.4 and 118.0 (Ar-$\underline{C}$H), 112.9 and 112.5 (Ar-$\underline{C}$H), 110.1 and 110.0 (Ar-$\underline{C}$H), 75.5 and 75.3 (2-$\underline{C}H_2$), 66.0 and 65.9 (2-C), 59.2 (ArO$\underline{C}H_3$), 55.1 ($CH_2O\underline{C}H_3$), 55.1 and 54.7 (5-C), 38.3, 38.1, 37.8, 37.3, 36.9, 31.9 and 26.6 (4x$\underline{C}H_2$), 32.2 and 28.6 (4'-$\underline{C}H_3$), 25.8 and 25.7 ($\underline{C}H_2$), and 22.0 and 21.9 ($\underline{C}H_2$); MS(EI low eV, m/z) 330 (M^+, 51%) and 285 (100); Analysis (Found: C, 72.3%; H, 9.15; N, 8.56, $C_{20}H_{30}N_2O_2$ requires: C, 72.7; H, 9.17; N, 8.48%).

*(2*R, cis/trans*)-4-(3-methoxyphenyl)-2,4-dimethylcyclo-hexanone* (94)

n-Butyl lithium (1.6 M, 45.5 cm^3) was added dropwise over a period of 1 h to a stirred slurry of potassium *t*-butoxide (8.2 g, 73.1 mmol) and dry diisopropylamine (10.2 cm^3, 7.4 g, 72.8 mmol), at -78°C and under an argon atmosphere. The suspension was then stirred at -78°C for 1 h. A solution of the chiral hydrazone (93) (21.8 g, 65.9 mmol) in dry ether (50 cm^3) was added over a period of 30 min, at -78°C. After stirring at -78°C for 10 h, the suspension was cooled to -110°C and a solution of methyl tosylate (14.77 g, 79.3 mmol) in dry ether (30 cm^3) was added over a period of 30 min. Stirring was continued at -110°C for 2 h before the reaction was allowed to warm to room temperature overnight. The suspension was poured into a mixture of water (200 cm^3) and ether (500 cm^3), separated and the aqueous phase extracted with ether (3x200 cm^3). The combined organic layers were washed with saturated brine (100 cm^3), dried (Na_2SO_4) and evaporated under reduced pressure to give a pale yellow oil. This residue was dissolved in iodomethane (25 cm^3) and heated at 40°C in a sealed tube for 16 h. After cooling, the solution was evaporated under reduced pressure to give a brown oil. The brown oil was stirred vigorously with a mixture of *n*-pentane (400 cm^3) and 2.5 M hydrochloric acid (250 cm^3) for 15 min. The *n*-pentane was then separated off and replaced with a fresh portion of *n*-pentane (400 cm^3), and the mixture stirred vigorously for a further 15 min. This process was repeated twice more and the combined *n*-pentane fractions were dried (Na_2SO_4) and evaporated under reduced pressure to give a colourless oil. Purification by "suction flash" column chromatography on silica gel, eluting with ethyl

acetate/60-80°C petroleum ether (3:47) gave the *trans*-title compound (78) (5.74 g, 37%), the *cis*-title compound (79) (1.91 g, 13%) and a mixture of the two, (78) and (79), (1.68 g, 11%) as colourless oils. *Trans*- (78): $[\alpha]_D^{18°C}$ +18.1° (c 1.3 in $CHCl_3$); IR(neat) ν_{max} 2940, 2900sh, 2860, 1700 (CO), 1590, 1570, 1480sh, 1450, 1420, 1280, 1230, 1040, 870, 780 and 690 cm^{-1}; ^1H n.m.r. ($CDCl_3$) δ_H 7.33 (1 H, t, *J* 8.0 Hz, 5'-H), 7.07 (1 H, ddd, *J* 8.0, 2.2 and 0.7 Hz, 6'-H), 7.02 (1 H, t, *J* 2.2 Hz, 2'-H), 6.80 (1 H, ddd, *J* 8.0, 2.2 and 0.7 Hz, 4'-H), 3.83 (3 H, s, $OC\underline{H}_3$), 2.65-2.53 (2 H, m, 2-H_{ax} and 6-H_{ax}), 2.41-2.27 (3 H, m, 6-H_{eq}, 5-H_{eq} and 3-H_{eq}), 1.84 (1 H, td, *J* 13.4 and 5.3 Hz, 5-H_{ax}), 1.60 (1 H, t, *J* 13.4 Hz, 3-H_{ax}), 1.21 (3 H, s, 4-$C\underline{H}_3$) and 1.01 (3 H, d, *J* 6.6 Hz, 2-$C\underline{H}_3$); ^{13}C n.m.r. ($CDCl_3$) δ_C 212.8 (CO), 160.1 (3'-C), 147.2 (1'-C), 129.8 (Ar-$\underline{C}$H), 118.1 (Ar-$\underline{C}$H), 112.9 (Ar-$\underline{C}$H), 110.2 (Ar-$\underline{C}$H), 55.1 ($O\underline{C}H_3$), 46.7 ($\underline{C}H_2$), 41.3 (2-C), 39.2 (4-C), 38.6 ($\underline{C}H_2$), 37.9 ($\underline{C}H_2$), 33.6 (4-$\underline{C}H_3$) and 14.3 (2-$\underline{C}H_3$); MS(m/z) 232 (*M*+, 36%) and 148 (100); Analysis (Found: C, 77.4; H, 8.85, $C_{15}H_{20}O_2$ requires: C, 77.5; H, 8.69%); Enantiomeric excess 76% (±2%, determined by ^1H n.m.r. in $CDCl_3$ using 0.060g TFAE and 0.010g sample, splitting observed in singlet at 1.2 ppm). *Cis*- (79): $[\alpha]_D^{18°C}$ +4.0° (c 0.3 in $CHCl_3$); IR(neat) ν_{max} 2960, 2920, 2870, 2830, 1710 (CO), 1600, 1580, 1480, 1450, 1420, 1290, 1260, 1050, 780 and 700 cm^{-1}; ^1H n.m.r. ($CDCl_3$) δ_H 7.26 (1 H, t, *J* 8.0 Hz, 5'-H), 7.00-6.97 (1 H, m, 6'-H), 6.94 (1 H, t, *J* 2.2 Hz, 2'-H), 6.76 (1 H, dd, *J* 8.0 and 2.2 Hz, 4'-H), 3.81 (3 H, s, $OC\underline{H}_3$), 2.75-2.59 (2 H, m, 2-H_{ax} and 6-H_{ax}), 2.41 (1 H, ddd, *J* 14.6, 4.6 and 2.8 Hz, 6-H_{eq}), 2.23-2.09 (3 H, m, 5-H_{ax}, 5-H_{eq} and 3-H_{eq}), 1.80 (1 H, t, *J* 13.3 Hz, 3-H_{ax}), 1.59 (3 H, s, 4-$C\underline{H}_3$) and 1.06 (3 H, d, *J* 6.4 Hz, 2-$C\underline{H}_3$); ^{13}C n.m.r. ($CDCl_3$) δ_C 212.8 (CO), 159.6 (3'-C), 151.4 (1'-C), 129.2 (Ar-$\underline{C}$H), 117.4 (Ar-$\underline{C}$H), 111.9 (Ar-$\underline{C}$H), 110.4 (Ar-$\underline{C}$H), 55.1 ($O\underline{C}H_3$), 47.4 ($\underline{C}H_2$),

40.8 (2-C), 38.4 ($\underline{C}H_2$), 38.3 (4-C), 38.0 ($\underline{C}H_2$), 24.4 (4-$\underline{C}H_3$) and 14.5 (2-$\underline{C}H_3$); MS(m/z) 232 (M^+, 73%), 175 (21), 161 (38) and 148 (100); Analysis (Found: C, 77.3; H, 8.79, $C_{15}H_{20}O_2$ requires: C, 77.5; H, 8.69%).

4-(3-Methoxyphenyl)-2,4-dimethylcyclohexanone (94) *via an ozonolytic hydrazone cleavage*

A solution of the dimethyl chiral hydrazone (77) (0.20 g, 0.58 mmol) in dichloromethane (3 cm^3) was cooled to -78°C, under a nitrogen atmosphere, and ozone (180 V, 7.5 psi O_3) was bubbled through for 3 h. After the solution had turned a blue/green colour, nitrogen was bubbled through the solution while it was allowed to warm to room temperature. The solution was then evaporated under reduced pressure to give a yellow oil. Purification by distillation using a Kugelruhr apparatus gave impure title compound as a yellow oil (0.020 g, 15%). b.p. 120°C (Kugelruhr) at 0.05 mmHg. The spectral details were identical with those described previously for these compounds (see p.73).

4-(3-Methoxyphenyl)-2,4-dimethyl-2-cyclohexen-1-one (98)

A 40% methanolic solution of benzyltrimethylammonium hydroxide (0.8 cm^3, 1.9mmol) was added dropwise, over a period of 20 min, to a stirred solution of the aldehyde (88) (1.0 g, 6.1 mmol) and ethyl vinyl ketone (0.56 g, 6.8mmol) in *t*-butanol (5 cm^3) at 0°C under a nitrogen atmosphere. The reaction was stirred at room temperature for 2.5 h, then quenched on ice (25 g) and extracted with ether (3x15 cm^3). The organic portions were combined, washed with saturated brine (10 cm^3), dried (Na_2SO_4) and evaporated under reduced pressure to give

a pale yellow oil. Purification by "flash" column chromatography on silica gel, eluting with ethyl acetate/*n*-hexane (1:9), gave the title compound as a pale yellow oil (1.13 g, 80%). IR(neat) ν_{max} 2960, 2920sh, 2860sh, 2840, 1670 (CO), 1600, 1580, 1480, 1440, 1420, 1360, 1250, 1040, 880, 780 and 700 cm^{-1}; ^1H n.m.r. ($CDCl_3$) δ_H 7.26 (1H, t, *J* 8.0 Hz, 5'-H), 6.91 (1 H, ddd, *J* 7.9, 2.0 and 0.9 Hz, 6'-H), 6.87 (1 H, t, *J* 2.0 Hz, 2'-H), 6.78 (1 H, ddd, *J* 8.0, 2.0 and 0.9 Hz, 4'-H), 6.68 (1 H, q, *J* 1.3 Hz, 3-H), 3.80 (3 H, s, $OC\underline{H}_3$), 2.40-2.00 (4 H, m, 5- and 6-H), 1.88 (3 H, d, *J* 1.3 Hz, 2-$C\underline{H}_3$) and 1.51 (3 H, s, 4-$C\underline{H}_3$); ^{13}C n.m.r. ($CDCl_3$) δ_C 199.4 (CO), 159.5 (3'-C), 151.8 (3-C), 147.5 (1'-C), 134.3 (2-C), 129.2 (Ar-$\underline{C}$H), 118.4 (Ar-$\underline{C}$H), 112.9 (Ar-$\underline{C}$H), 110.6 (Ar-$\underline{C}$H), 54.9 ($O\underline{C}H_3$), 40.7 (4-C), 37.8 (6-C), 34.4 (5-C), 28.0 (4-$\underline{C}H_3$) and 15.8 (2-$\underline{C}H_3$); MS(m/z), 230 (*M*$^+$, 100%), 215 (25), 202 (21), 199 (15), 187 (41) and 173 (73); Analysis (Found: C, 78.5; H, 7.83, $C_{15}H_{18}O_2$ requires: C, 78.2; H, 7.88%).

4-(3-Methoxyphenyl)-2,4-dimethylcyclohexanone (94)

A solution of the dimethylcyclohexenone (98) (1.10 g, 4.78 mmol) in glacial acetic acid (10 cm^3) was hydrogenated in the presence of a 10% palladium on charcoal catalyst (0.11 g) at atmospheric pressure until hydrogen uptake ceased. The reaction mixture was filtered through a bed of Celite to remove the catalyst. A mixture of *n*-hexane (100 cm^3) and water (100 cm^3) was added to the filtrate and the organic layer separated. The aqueous layer was extracted with a mixture of *n*-hexane/ether (1:1, 3x60 cm^3). All the organic portions were combined, washed with saturated aqueous sodium bicarbonate solution (40 cm^3), saturated brine (10 cm^3), dried ($MgSO_4$) and evaporated under reduced pressure to give a pale yellow oil (0.37 g).

The filter bed was washed with ethanol (2x30 cm^3) and this filtrate was evaporated under reduced pressure to give a yellow oil. This residue was dissolved in ethyl acetate (20 cm^3) and the solution washed with water (20 cm^3). The aqueous layer was washed with ethyl acetate (2x20 cm^3). The combined organic portions were washed with saturated aqueous sodium bicarbonate solution (10 cm^3), dried ($MgSO_4$) and evaporated under reduced pressure to give a yellow oil (0.68 g). These two residues were combined and purified by "flash" column chromatography on silica gel, eluting with ethyl acetate/*n*-hexane (2:23) gave the *trans*-title compound (78) as a colourless oil (0.21 g, 19%), the *cis*-title compound (79) as a colourless oil (0.46 g, 41%) and a mixture of the *cis/trans*-title compound as a colourless oil (0.10 g, 9%). The spectral details were identical with those described previously for these compounds (p.73).

*(2*S, E/Z*)-2-Methoxymethyl-*N*-[4-(3-methoxyphenyl)-4-methyl-2-cyclohexen-1-ylidene]-1-pyrrolidinamine* (134)

A solution of the cyclohexenone (76) (1.58 g, 7.32 mmol) and (*S*)-1-amino-2-methoxymethylpyrrolidine (1.0 g, 7.64 mmol) in toluene (20 cm^3) was heated under reflux in a Dean-Stark apparatus, in an argon atmosphere, for 12 h. After cooling, the solution was washed with water (5 cm^3), dried (Na_2SO_4) and evaporated under reduced pressure to give a brown oil. Distillation using a Kugelruhr apparatus gave the title compound as a yellow oil (2.33 g, 97%). b.p. 160°C (Kugelruhr) at 0.05 mmHg. IR(0.5% solution in $CHBr_3$) ν_{max} 2960, 2940, 2870, 2830, 1600, 1580, 1485, 1460, 1430, 1260, 1050 and 780 cm^{-1}; ^1H n.m.r. ($CDCl_3$) δ_H (mixture of 4 stereomers/diastereomers) 7.28-7.21 (1 H, m, 5''-H), 6.97-6.74 (3 H, m, 2''-, 4''- and 6''-H), 6.33-6.09 (2 H, m,

2'- and 3'-H), 3.82, 3.81, 3.80 and 3.79 (3 H, 4xs, Ar-OC$\underline{H}_3$), 3.53-3.20 (7 H, m, C$\underline{H}_2$OC$\underline{H}_3$, 2-H and 5-H), 2.68-1.61 (9 H, m, 4xC$\underline{H}_2$ and 5-H), 1.48, 1.47, 1.46 and 1.43 (3 H, 4xs, 4'-C$\underline{H}_3$); Analysis (Found: C, 73.3; H, 8.57; N, 8.52, $C_{20}H_{28}N_2O_2$ requires: C, 73.1; H, 8.61; N, 8.53%).

(6R)-(+)-4-(3-Methoxyphenyl)-4,6-dimethyl-2-cyclohexen-1-one (103)

n-Butyl lithium (1.2 M, 0.56 cm^3, 0.69 mmol) was added dropwise over a period of 1 h to a stirred slurry of potassium *t*-butoxide (0.077 g, 0.69 mmol) and dry diisopropylamine (0.1 cm^3, 0.07 g, 0.69 mmol) in dry tetrahydrofuran (5 cm^3), at -78°C and under an argon atmosphere. The suspension was then stirred at -78°C for 1 h. A solution of the chiral hydrazone (134) (0.21 g, 0.65 mmol) in dry tetrahydrofuran (1 cm^3) was added dropwise at -78°C. After stirring at -78°C for 5 h, the suspension was cooled to -110°C and a solution of methyl tosylate (0.14 g, 0.72 mmol) in dry tetrahydrofuran (1 cm^3) over a period of 15 min. Stirring was continued at -110°C for 30 min before the reaction was allowed to warm to room temperature overnight. The suspension was poured into a mixture of water (5 cm^3) and ether (15 cm^3), separated, and the aqueous phase extracted with ether (3x5 cm^3). The combined organic layers were washed with saturated brine (5 cm^3), dried (Na_2SO_4) and evaporated under reduced pressure to give a pale yellow oil (0.19 g). This residue was dissolved in iodomethane (5 cm^3) and heated at 40°C in a sealed tube for 16 h. After cooling, the solution was evaporated under reduced pressure to give a brown oil. The brown oil was stirred vigorously with a mixture of *n*-pentane (15 cm^3) and 3 M hydrochloric acid (15 cm^3) for 15 min. The *n*-pentane was then separated off and replaced

with a fresh portion of *n*-pentane (15 cm^3), and the mixture stirred vigorously for a further 15 min. This process was repeated twice more and the combined *n*-pentane fractions were dried (Na_2SO_4), and evaporated under reduced pressure to give a brown oil (0.066 g). Purification by "flash" column chromatography on silica gel, eluting with ethyl acetate/60-80°C petroleum ether (1:9) gave the title compound as a pale yellow oil (0.021 g, 16%). $[\alpha]_D^{18°C}$ +34.8° (c 0.6 in $CHCl_3$); IR(neat) ν_{max} 2960, 2930, 2870, 1680 (α,β-unsaturated CO), 1605, 1580, 1480, 1450, 1430, 1370, 1290, 1260, 1050, 815, 780 and 700 cm^{-1}; ^1H n.m.r. ($CDCl_3$) δ_H (3:2 mixture of diastereomers) 7.33-7.24 (1 H, m, 5'-H), 6.98-6.76 (4 H, m, 2'-, 4'-, 6'- and 2-H), 6.14 and 6.05 (1 H, 2xd, *J* 10.0 Hz, 3-H), 3.81 (3 H, s, $OC\underline{H}_3$), 2.89-2.60 (0.6 H, m, 6-H of one diastereomer), 2.34-1.86 (2.4 H, m, 5-H and 6-H of other diastereomer), 1.64 and 1.49 (3 H, 2xs, 4-$C\underline{H}_3$), 1.13 and 1.02 (3 H, 2xd, *J* 6.6 Hz, 6-$C\underline{H}_3$); Analysis (Found: C, 78.1; H, 8.18, $C_{15}H_{18}O_2$ requires: C, 78.2; H, 7.89%).

*(2*R-trans, E*)-(+)-4-(3-Methoxyphenyl)-2,4-dimethylcyclo-hexanone oxime* (102)

A mixture of the *trans*-dimethylcyclohexanone (78) (5.68 g, 24.4 mmol), hydroxylamine hydrochloride (6.79 g, 97.7 mmol) and sodium acetate (8.02 g, 97.7mmol) in 80% methanol (50 cm^3) was stirred at room temperature for 18 h. The reaction mixture was poured into water (100 cm^3) and extracted with ethyl acetate (4x50 cm^3). The combined organic layers were washed with saturated aqueous sodium bicarbonate solution (30 cm^3), saturated brine (25 cm^3), dried (Na_2SO_4) and evaporated under reduced pressure to give a colourless solid. Recrystallization from ether/60-80°C petroleum ether gave the

title compound as a colourless crystalline solid (5.13 g, 85%). m.p. 94-95°C. $[\alpha]_D^{18°C}$ +3.5° (c 1.1 in $CHCl_3$); IR(nujol mull) ν_{max} 3250br, 1675w, 1610, 1580, 1480, 1290, 1240, 1050, 945, 870, 780, 700 and 675 cm^{-1}; ^1H n.m.r. ($CDCl_3$) δ_H 9.80 (1 H, br s, OH), 7.29 (1 H, t, *J* 8.0 Hz, 5'-H), 7.00 (1 H, d, *J* 8.0 Hz, 6'-H), 6.96 (1 H, d, *J* 2.2 Hz, 2'-H), 6.75 (1 H, dd, *J* 8.0 and 2.2 Hz, 4'-H), 3.81 (3 H, s, $OC\underline{H}_3$), 3.27 (1 H, dt, *J* 14.1 and 2.8 Hz, $6\text{-}H_{eq}$), 2.50-2.38 (2 H, m, $3\text{-}H_{eq}$ and $5\text{-}H_{eq}$), 2.38-2.20 (1 H, m, $2\text{-}H_{ax}$), 1.82-1.49 (2 H, m, $5\text{-}H_{ax}$ and $6\text{-}H_{ax}$), 1.43 (1 H, t, *J* 13.3 Hz, $3\text{-}H_{ax}$), 1.15 (3 H, s, $4\text{-}C\underline{H}_3$) and 1.09 (3 H, d, *J* 6.4 Hz, $2\text{-}C\underline{H}_3$); ^{13}C n.m.r. ($CDCl_3$) δ_C 162.5 (CN), 159.9 (3'-C), 147.8 (1'-C), 129.6 (Ar-<u>C</u>H), 118.4 (Ar-<u>C</u>H), 113.0 (Ar-<u>C</u>H), 110.0 (Ar-<u>C</u>H), 55.1 ($O\underline{C}H_3$), 47.0 ($\underline{C}H_2$), 39.0 (4-C), 36.4 ($\underline{C}H_2$), 34.1 ($4\text{-}\underline{C}H_3$), 33.5 ($2\text{-}\underline{C}H_3$), 21.3 ($\underline{C}H_2$) and 16.3 ($2\text{-}\underline{C}H_3$); MS(m/z) 247 (*M*$^+$, 52%), 230 (25, *M*-OH), 149 (56) and 148 (28); Analysis (Found: C, 72.4; H, 8.54; N, 5.81, $C_{15}H_{21}NO_2$ requires: C, 72.8; H, 8.57; N, 5.66%); Enantiomeric excess 76% (±2%, determined by ^1H n.m.r. in $CDCl_3$ using 0.035g TFAE and 0.010g sample, splitting observed in singlet at 1.0 ppm).

*(2*R-cis, E*)-(+)-4-(3-Methoxyphenyl)-2,4-dimethylcyclo-hexanone oxime* (101)

A mixture of the *cis*-dimethylcyclohexanone (79) (1.40 g, 6.0 mmol), hydroxylamine hydrochloride (1.47 g, 21.2 mmol) and sodium acetate (2.48 g, 30.2mmol) in 80% methanol (25 cm^3) was stirred at room temperature for 18 h. The reaction mixture was poured into water (25 cm^3) and extracted with ethyl acetate (4x30 cm^3). The combined organic layers were washed with saturated aqueous sodium bicarbonate solution (15 cm^3), saturated brine (15 cm^3), dried (Na_2SO_4) and evaporated under reduced pressure to give a colourless

solid. Recrystallization from ether/60-80°C petroleum ether gave the title compound as a colourless crystalline solid (1.25 g, 84%). m.p. 105-106°C. $[\alpha]_D^{18°C}$ +48.4° (c 1.0 in $CHCl_3$); IR(nujol mull) ν_{max} 3200br, 1670w, 1600, 1590sh, 1470, 1270, 1240, 1180, 1040, 940, 890, 780 and 700 cm^{-1}; ^1H n.m.r. ($CDCl_3$) δ_H 9.10 (1 H, br s, OH), 7.25 (1 H, t, *J* 8.0 Hz, 5'-H), 6.97 (1 H, m, 6'-H), 6.92 (1 H, t, *J* 2.2 Hz, 2'-H), 6.74 (1 H, dd, *J* 8.0 and 2.2 Hz, 4'-H), 3.81 (3 H, s, $OC\underline{H}_3$), 3.39 (1 H, m, 6-H_{eq}), 2.68-2.58 (1 H, m, 2-H_{ax}), 2.10-1.75 (4 H, m, 3-H_{eq}, 5-H_{ax}, 5-H_{eq} and 6-H_{ax}), 1.64 (1 H, t, *J* 13.0 Hz, 3-H_{ax}), 1.44 (3 H, s, 4-$C\underline{H}_3$) and 1.14 (3 H, d, *J* 6.5 Hz, 2-$C\underline{H}_3$); ^{13}C n.m.r. ($CDCl_3$) δ_C 162.3 (CN), 159.5 (3'-C), 152.3 (1'-C), 129.1 (Ar-$\underline{C}H$), 117.5 (Ar-$\underline{C}H$), 111.8 (Ar-$\underline{C}H$), 110.4 (Ar-$\underline{C}H$), 55.1 ($O\underline{C}H_3$), 47.4 ($\underline{C}H_2$), 37.4 (4-C), 36.7 ($\underline{C}H_2$), 33.1 (4-$\underline{C}H_3$), 24.4 (2-$\underline{C}H_3$), 20.8 ($\underline{C}H_2$) and 16.5 (2-$\underline{C}H_3$); MS(m/z) 247 (*M*$^+$, 100), 230 (28, *M*-OH), 205 (20), 148 (33) and 121 (31); Analysis (Found: C, 72.7; H, 8.62; N, 5.61, $C_{15}H_{21}NO_2$ requires: C, 72.8; H, 8.57; N, 5.66%); Enantiomeric excess 60% (±4%, determined by ^1H n.m.r. in $CDCl_3$ using 0.050g TFAE and 0.010g sample, splitting observed in singlet at 1.4 ppm).

Crystal Data.-$C_{15}H_{21}NO_2$, *M* = 247.37. Triclinic, *a* = 6.437 (2), *b* = 10.830 (2), *c* = 11.366 (2) Å, α = 113.47 (2), β = 98.99 (2), γ = 101.65 (2), *V* = 686.75 Å^3 (by least squares refinement on diffractometer angles for 12 automatically centred reflections, λ = 0.71069 Å), space group $P\bar{1}$, *Z* = 2, D_X = 1.19 g cm^{-3}. Colourless rods. Crystal dimensions: 0.3 x 0.3 x 0.3 mm, μ(Mo-K_α) = 0.44 cm^{-1}.

Data Collection and Processing.[62]-Hilger and Watts Y290 4-circle diffractometer, graphite monochromated Mo-K_α radiation; 1837 reflections were measured ($2 \leq \Theta \leq 22°$), 1471 unique and 1151 observed with $I > 3\sigma(I)$. No crystal decay was detected during data

collection.

Structure Analysis and Refinement.-Direct methods[63] were successful in locating all non-hydrogen atoms. The structure was refined using SHELX76.[64] The weighting scheme $w = 8.1764\ [\sigma^2(F_o) + 0.08\ F_o^2]$, with $\sigma(F_o)$ from counting statistics[65,66,67] gave satisfactory agreement analyses. Final R and R_w values are 0.071 and 0.074. Sources of scattering factor data are given in refs. 65-67.

(5S-trans)-(-)-Hexahydro-5-(3-methoxyphenyl)-5,7-dimethyl-2-azepinone (109)

Phosphorus oxychloride (15 cm^3) was added dropwise to a stirred solution of the *trans*-oxime (102) (7.41 g, 30mmol) in dry pyridine (35 cm^3) at 0°C, under a nitrogen atmosphere. After stirring at 0°C for 5 h, the solution was carefully poured onto ice (250 g) and left for 1 h. Concentrated hydrochloric acid (37 cm^3) was added slowly and the resulting mixture extracted with ethyl acetate (4x100 cm^3). The combined organic layers were washed with saturated aqueous sodium bicarbonate solution (100 cm^3), saturated brine (50 cm^3), dried (Na_2SO_4) and evaporated under reduced pressure to give a yellow oil. Crystallization from *n*-pentane gave the title compound as a white crystalline solid (5.25 g, 71%). The mother liquor was evaporated under reduced pressure and purified by "suction flash" column chromatography on silica gel, eluting with ethyl acetate/60-80°C petroleum ether (4:1) to give the title compound as a colourless crystalline solid (0.80 g, 11%). m.p. 133-134°C. $[\alpha]_D^{18°C}$ -29.6° (c 1.2 in $CHCl_3$); IR(nujol mull) ν_{max} 3200 (NH), 3080 (NH), 1670 (CO), 1640sh, 1610, 1580, 1295, 1250, 1230, 1180, 1050, 880, 810, 780 and 700 cm^{-1}; ^1H n.m.r. ($CDCl_3$) δ_H 7.33 (1 H, t, J 8.0 Hz, 5'-H), 6.85 (1 H,

d, *J* 8.0 Hz, 6'-H), 6.83-6.75 (2 H, m, 2'- and 4'-H), 6.29 (1 H, br s, NH), 3.82 (3 H, s, $OC\underline{H}_3$, 3.56-3.40 (1 H, m, 7-H), 2.54-2.24 (4 H, m, 3-H, 1x4-H and 1x6-H), 1.82-1.66 (1 H, m, 1x4-H), 1.59 (1 H, dd, *J* 14.8 and 9.5 Hz, 1x6-H), 1.24 (3 H, d, *J* 6.8 Hz, 7-$C\underline{H}_3$) and 1.14 (3 H, s, 5-$C\underline{H}_3$); ^{13}C n.m.r. ($CDCl_3$) δ_C 177.3 (CO), 159.9 (3'-C), 147.4 (1'-C), 129.7 (Ar-$\underline{C}H$), 118.5 (Ar-$\underline{C}H$), 113.3 (Ar-$\underline{C}H$), 110.1 (Ar-$\underline{C}H$), 55.1 ($O\underline{C}H_3$), 48.3 ($\underline{C}H_2$), 45.0 (7-C), 41.7 (5-C), 35.3 ($\underline{C}H_3$), 33.5 ($\underline{C}H_2$), 32.7 ($\underline{C}H_2$) and 22.3 ($\underline{C}H_3$); MS(m/z) 247 (M^+, 36%), 191 (16) 148 (30) and 99 (100); Analysis (Found: C, 72.9; H, 8.66; N, 5.58, $C_{15}H_{21}NO_2$ requires: C, 72.8; H, 8.57; N, 5.66%); Enantiomeric excess 80% (±4%, determined by ^1H n.m.r. in $CDCl_3$ using 0.030g TFAE and 0.010g sample, splitting observed in singlet at 1.1 ppm).

(5S-cis)-(-)-Hexahydro-5-(3-methoxyphenyl)-5,7-dimethyl-2-azepinone (110)

Phosphorus oxychloride (3.4 cm^3) was added dropwise to a stirred solution of the *cis*-oxime (101) (1.14 g, 4.6mmol) in dry pyridine (7.5 cm^3) at 0°C, under a nitrogen atmosphere. After stirring at 0°C for 5 h, the solution was carefully poured onto ice (50 g) and left for 1 h. Concentrated hydrochloric acid (8 cm^3) was added slowly and the resulting mixture extracted with ethyl acetate (4x30 cm^3). The combined organic layers were washed with saturated aqueous sodium bicarbonate solution (10 cm^3), saturated brine (10 cm^3), dried (Na_2SO_4) and evaporated under reduced pressure to give a yellow oil. Crystallization from *n*-pentane gave the title compound as a colourless crystalline solid (8.83 g, 73%). m.p. 113-114°C. $[\alpha]_D^{18°C}$ -1.1° (c 1.2 in $CHCl_3$); IR(nujol mull) ν_{max} 3200 (NH), 3080 (NH), 1640 (CO), 1600, 1570, 1430, 1300, 1245, 1150, 860, 810, 780 and 700 cm^{-1}; ^1H n.m.r.

($CDCl_3$) δ_H 7.25 (1 H, t, *J* 8.0 Hz, 5'-H), 6.97 (1 H, d, *J* 7.9 Hz, 6'-H), 6.92 (1 H, t, *J* 2.0 Hz, 2'-H), 6.75 (1 H, dd, *J* 8.0 and 2.0 Hz, 4'-H), 6.55 (1 H, br s, NH), 3.80 (4 H, s, 7-H and OCH_3), 2.75 (1 H, t, *J* 13.6 Hz, 3-H), 2.38 (1 H, dd, *J* 13.6 and 7.7 Hz, 3-H), 2.06 (1 H, t, *J* 13.6 Hz, 4-H), 1.87 (1 H, dd, *J* 14.5 and 10.2 Hz, 6-H), 1.81 (1 H, dd, *J* 13.6 and 7.7 Hz, 4-H), 1.69 (1 H, d, *J* 14.5 Hz, 6-H), 1.43 (3 H, s, 5-CH_3) and 1.25 (3 H, d, *J* 6.6 Hz, 7-CH_3); ^{13}C n.m.r. ($CDCl_3$) δ_C 177.2 (CO), 159.5 (3'-C), 152.0 (1'-C), 129.1 (Ar-CH), 117.5 (Ar-CH), 112.0 (Ar-CH), 110.5 (Ar-CH), 55.1 (OCH_3), 49.7 (CH_2), 44.2 (7-C), 39.6 (5-C), 34.7 (CH_2), 32.1 (CH_2), 23.8 (CH_3) and 22.7 (CH_3); MS(m/z) 247 (*M*$^+$, 79%), 204 (30, *M*-CONH) and 189 (24); Analysis (Found: C, 73.0; H, 8.66; N, 5.68, $C_{15}H_{21}NO_2$ requires: C, 72.8; H, 8.57; N, 5.66%).

*(5*S-trans*)-(-)-Hexahydro-5-(3-methoxyphenyl)-1,5,7-trimethyl-2-azepinone* (80)

Dry tetrahydrofuran (50 cm^3) was added to a mixture of the *trans*-caprolactam (109) (6.05 g, 24.5 mmol) and sodium hydride (97% oil dispersion, 1.21 g, 48.9 mmol), and the suspension was stirred at room temperature for 24 h, under a nitrogen atmosphere. Iodomethane (7.6 cm^3, 17.4 g, 122 mmol) was added dropwise and the suspension was stirred at room temperature for a further 48 h. After quenching on ice (100 g), the mixture was extracted with ethyl acetate (4x50 cm^3), the organic layers combined, washed with saturated brine (30 cm^3), dried (Na_2SO_4) and evaporated under reduced pressure to give the pure title compound as a pale yellow oil (6.35 g, 99%). $[\alpha]_D^{18°C}$ -1.8° (c 4.3 in $CHCl_3$); IR(neat) ν_{max} 2960, 2880sh, 2840, 1640 (CO), 1600, 1570, 1490, 1450, 1420, 1390, 1290, 1250, 1050, 870, 780 and 700 cm^{-1}; ^1H n.m.r. ($CDCl_3$) δ_H 7.31 (1 H, t, *J* 8.0 Hz, 5'-H), 6.90 (1 H,

ddd, *J* 8.0, 2.0 and 0.8 Hz, 6'-H), 6.84 (1 H, t, *J* 2.0 Hz, 2'-H), 6.78 (1 H, ddd, *J* 8.0, 2.0 and 0.8 Hz, 4'-H), 3.82 (3 H, s, $OC\underline{H}_3$), 3.67 (1 H, p, *J* 8.0 Hz, 7-H), 2.86 (3 H, s, $NC\underline{H}_3$), 2.62 (1 H, t, *J* 12.8 Hz, 3-H), 2.56-2.37 (2 H, m, 3- and 4-H), 2.21 (1 H, dd, *J* 14.8 and 1.8 Hz, 6-H), 1.70-1.56 (2 H, m, 6- and 4-H), 1.30 (3 H, d, *J* 8.0 Hz, 7-$C\underline{H}_3$) and 1.12 (3 H, s, 5-$C\underline{H}_3$); ^{13}C n.m.r. ($CDCl_3$) δ_C 175.6 (CO), 159.9 (3'-C), 147.5 (1'-C), 129.7 (Ar-$\underline{C}H$), 118.5 (Ar-$\underline{C}H$), 113.1 (Ar-$\underline{C}H$), 110.2 (Ar-$\underline{C}H$), 55.0 ($O\underline{C}H_3$), 49.8 (7-C), 45.9 ($\underline{C}H_2$), 41.5 (5-C), 34.6 ($\underline{C}H_3$), 34.3 ($\underline{C}H_2$), 33.0 ($\underline{C}H_2$), 27.3 ($\underline{C}H_3$) and 20.5 ($\underline{C}H_3$); MS(m/z) 261 (*M*+, 33%), 246 (2, *M*-CH_3), 204 (5, *M*-$CONCH_3$) and 113 (100); Acc. MS(m/z) (Found: 261.1737 (*M*+, 100%), $C_{16}H_{23}NO_2$ requires: 261.1727, +3.8 ppm).

(cis)-Hexahydro-5-(3-methoxyphenyl)-1,5,7-trimethyl-2-azepinone (116)

Dry tetrahydrofuran (20 cm^3) was added to a mixture of the *cis*-caprolactam (110) (0.81 g, 3.3 mmol) and sodium hydride (97% oil dispersion, 0.20 g, 8.1 mmol), and the suspension was stirred at room temperature for 1 h, under a nitrogen atmosphere. Iodomethane (1.25 cm^3, 2.85 g, 20 mmol) was added dropwise and the suspension was stirred at room temperature for a further 24 h. After quenching on ice (20 g), the mixture was extracted with dichloromethane (4x10 cm^3), the organic layers combined, washed with saturated brine (10 cm^3), dried (Na_2SO_4) and evaporated under reduced pressure to give the pure title compound as a pale yellow oil (0.82 g, 96%). IR(neat) ν_{max} 2960, 2930, 2840, 1625 (CO), 1600sh, 1580, 1450, 1420, 1250, 1100, 1050, 875, 780, 730 and 700 cm^{-1}; ^1H n.m.r. ($CDCl_3$) δ_H 7.25 (1 H, t, *J* 8.0 Hz, 5'-H), 6.94 (1 H, ddd, *J* 8.0, 2.0 and 0.7 Hz, 6'-H), 6.89 (1 H, t, *J* 2.0 Hz, 2'-H), 6.75 (1 H, ddd, *J* 8.0, 2.0 and 0.7 Hz, 4'-H), 4.10 (1 H, p,

J 7.4 Hz, 7-H), 3.81 (3 H, s, $OC\underline{H}_3$), 2.96-2.84 (1 H, m, 3-H), 2.90 (3 H, s, $NC\underline{H}_3$), 2.52 (1 H, ddd, *J* 14.5, 7.5 and 1.7 Hz, 3-H), 2.07-1.78 (3 H, m, 6- and 2x4-H), 1.57 (1 H, d, *J* 14.3 Hz, 6-H), 1.40 (3 H, s, 5-$C\underline{H}_3$) and 1.28 (3 H, d, *J* 7.4 Hz, 7-$C\underline{H}_3$); ^{13}C n.m.r. ($CDCl_3$) δ_C 175.2 (CO), 159.3 (3'-C), 151.6 (1'-C), 129.0 (Ar-$\underline{C}H$), 117.4 (Ar-$\underline{C}H$), 111.8 (Ar-$\underline{C}H$), 110.1 (Ar-$\underline{C}H$), 54.9 ($O\underline{C}H_3$), 49.0 (7-C), 46.5 ($\underline{C}H_2$), 39.1 (5-C), 34.9 ($\underline{C}H_2$), 32.4 ($\underline{C}H_2$), 27.5 ($\underline{C}H_3$), 24.9 ($\underline{C}H_3$) and 20.5 ($\underline{C}H_3$); MS(m/z) 261 (*M*$^+$, 46%), 246 (7, *M*-CH_3), 204 (24, *M*-$CONCH_3$) and 189 (26); Acc. MS(m/z) (Found: 261.1734 (*M*$^+$, 100%), $C_{16}H_{23}NO_2$ requires: 261.1727, +2.7 ppm).

(cis)-Benzyl hexahydro-5-(3-methoxyphenyl)-5,7-dimethyl-2-azepinone-1-carboxylate (113)

A solution of the *cis*-caprolactam (110) (0.05 g, 0.2 mmol) in dry tetrahydrofuran (3 cm^3) was added to sodium hydride (60% oil dispersion, 0.016 g, 0.4 mmol) and the resulting suspension was stirred at room temperature for 1 h, under a nitrogen atmosphere. Benzyl chloroformate (0.14 cm^3, 0.17 g, 1.0 mmol) was added dropwise and the suspension was heated under reflux for 8 h. After cooling, the suspension was poured onto ice (5 g) and extracted with dichloromethane (4x3 cm^3). The combined organic layers were washed with saturated brine (3 cm^3), dried (Na_2SO_4) and evaporated under reduced pressure to give a yellow oil. Purification by "flash" column chromatography on silica gel, eluting with a gradient of ethyl acetate/60-80°C petroleum ether (3:22 to 1:1 to 1:0), gave the title compound as a colourless oil (0.038 g, 49%) and the starting compound (110) as a colourless oil (0.010 g, 19%). IR(solution in $CHCl_3$) ν_{max} 2920, 2830sh, 1740sh (CO), 1700 (CO), 1600sh, 1580, 1450, 1380, 1250br,

1090, 1040 and 880 cm^{-1}; ^1H n.m.r. ($CDCl_3$) δ_H 7.42-7.31 (5 H, m, 5xPhH), 7.26 (1 H, t, *J* 7.9 Hz, 5'-H), 6.92 (1 H, ddd, *J* 7.9, 2.1 and 0.8 Hz, 6'-H), 6.87 (1 H, t, *J* 2.1 Hz, 2'-H), 6.75 (1 H, ddd, *J* 7.9, 2.1 and 0.8 Hz, 4'-H), 5.25 (2 H, s, $PhCH_2$), 4.40-4.32 (1 H, m, 7-H), 3.80 (3 H, s, OCH_3), 2.72 (2 H, ABXY, J_{AB} 16.6 Hz, J_{AX} 9.0 Hz, J_{AY} 2.2 Hz, J_{BX} 1.9 Hz and J_{BY} 10.3 Hz, 3-H), 2.36 (1 H, dd, *J* 15.3 and 9.4 Hz, 6-H), 2.22 (1 H, ddd, *J* 15.0, 9.0 and 1.9 Hz, 1x4-H), 1.89 (1 H, ddd, *J* 15.0, 10.3 and 2.2 Hz, 1x4-H), 1.82 (1 H, dd, *J* 15.3 and 2.0 Hz, 6-H), 1.33 (3 H, s, 5-CH_3) and 1.21 (3 H, d, 7-CH_3); MS(m/z) 381 (M^+, 20%), 247 (11), 198 (23), 167 (28) and 91 (100).

(cis)-Hexahydro-5-(3-methoxyphenyl)-5,7-dimethyl-1-(phenylmethyl)-2-azepinone (114)

A solution of the *cis*-caprolactam (110) (0.20 g, 0.8 mmol) in dry tetrahydrofuran (3 cm^3) was added to sodium hydride (60% oil dispersion, 0.065 g, 1.6 mmol) and the resulting suspension was stirred at room temperature for 1 h, under a nitrogen atmosphere. Benzyl bromide (0.19 cm^3, 0.28 g, 1.6 mmol) was added dropwise and the suspension was stirred at room temperature for 14 h. The suspension was poured onto ice (5 g) and extracted with dichloromethane (4x3 cm^3). The combined organic layers were washed with saturated brine (3 cm^3), dried (Na_2SO_4) and evaporated under reduced pressure to give a yellow oil. Purification by "flash" column chromatography on silica gel, eluting with ethyl acetate/60-80°C petroleum ether (1:1), gave the title compound as a colourless oil (0.14 g, 51%) and the starting compound (110) as a colourless oil (0.05 g, 25%). IR(neat) ν_{max} 3070, 2960, 2920sh, 2820, 1625 (CO), 1600sh, 1580, 1480sh, 1450, 1410, 1290, 1250, 1050, 940, 880, 750 and 700 cm^{-1}; ^1H

n.m.r. ($CDCl_3$) δ_H 7.34-7.19 (6 H, m, 5xPh$\underline{H}$ and 5'-H), 6.87 (1 H, ddd, J 8.1, 2.2 and 0.8 Hz, 4'-H), 4.65 (2 H, ABq, J_{AB} 15.6 Hz, Ph$C\underline{H}_2$), 4.18-4.04 (1 H, m, 7-H), 3.78 (3 H, s, $OC\underline{H}_3$), 2.67 (2 H, ABX, J_{AB} 13.5 Hz, J_{AX} 10.3 Hz and J_{BX} 8.1 Hz, 3-H), 2.15 (1 H, t, J 14.1 Hz, 1x6-H), 1.90 (2 H, ABX, J_{AB} 14.5 Hz, J_{AX} 10.3 Hz and J_{BX} 8.1 Hz, 4-H), 1.49 (1 H, d, J 14.1 Hz, 1x6-H), 1.35 (3 H, s, 5-$C\underline{H}_3$) and 1.15 (3 H, d, J 7.1 Hz, 7-$C\underline{H}_3$); MS(m/z) 337 (M^+, 67%), 322 (7, M-CH_3), 204 (10), 179 (20), 160 (23), 148 (23), 134 (25), 86 (100) and 84 (100); Acc. MS(m/z) (Found: 337.2075 (M^+, 100%), $C_{22}H_{27}NO_2$ requires: 337.2039, +10.0 ppm).

*(5S,7R)-(+)-5-(3-Methoxyphenyl)-5-methyl-7-(*N*-methyltrifluoroacetylamino)octan-2-one* (81)

Methyl lithium (1.4 M, 14.2 cm^3, 19.9 mmol) was added dropwise to a stirred solution of the methylcaprolactam (80) (5.2 g, 19.9 mmol) in dry tetrahydrofuran (100 cm^3) at 0°C, under a nitrogen atmosphere, and the mixture was stirred at room temperature for 2 h. After cooling to -23°C, trifluoroacetic anhydride (8.4 cm^3, 12.5 g, 59.7 mmol) was added dropwise and the solution was then allowed to warm to room temperature over the period of 1 h. The reaction was poured onto ice (200 g) and then extracted with ethyl acetate (4x75 cm^3). The combined organic layers were washed with water (50 cm^3), saturated brine (40 cm^3), dried (Na_2SO_4) and evaporated under reduced pressure to give a brown oil (12.5 g). Purification by "suction flash" column chromatography on silica gel, eluting with chloroform, gave the title compound as a pale yellow waxy solid (4.11 g, 55%) m.p. 79-80°C, and the starting compound (80) as a yellow oil (0.67 g, 13%). $[\alpha]_D^{18°C}$ +89.4° (c 1.3 in $CHCl_3$); IR(solution in $CHCl_3$) ν_{max} 2960, 2850, 1710sh (CO), 1680 (CO), 1600, 1580, 1480sh, 1450, 1410. 1290, 1140, 1100,

1090sh, 1050sh and 870 cm^{-1}; ^1H n.m.r. ($CDCl_3$) δ_H (1:9 mixture of rotomers) 7.19 (1 H, t, *J* 7.9 Hz, 5'-H), 6.82-6.69 (3 H, m, 2'-, 4'- and 6'-H), 4.77 (1 H, m, 7-H), 3.78 (3 H, s, $OC\underline{H}_3$), 2.65 (1 H, s, $NC\underline{H}_3$, minor rotomer), 2.39 (1 H, q, *J* 1.7 Hz, $NC\underline{H}_3$, major rotomer), 2.32-1.52 (6 H, m, 3-, 4- and 6-H), 1.99 (3 H, s, 1-H), 1.52 (3 H, s, $5\text{-}C\underline{H}_3$) and 1.08 (3 H, d, *J* 6.8 Hz, 8-H); MS(m/z) 373 (*M*$^+$, 28%), 303 (5), 302 (7), 175 (66), 154 (100) and 148 (89); Analysis (Found: C, 61.0; H, 7.05; N, 3.74, $C_{19}H_{26}F_3NO_3$ requires: C, 61.1; H, 7.03; N, 3.75%).

*(5*R**,7*R**)-5-(3-Methoxyphenyl)-5-methyl-7-(*N*-methylamino)-octan-2-one* (117)

Methyl lithium (1.4 M, 2.25 cm^3, 3.15 mmol) was added dropwise to a stirred solution of the methylcaprolactam (116) (0.82 g, 3.14 mmol) in dry tetrahydrofuran (20 cm^3) at 0°C, under a nitrogen atmosphere, and the mixture was stirred at room temperature for 2 h. The solution was poured onto a mixture of ice (10 g) and 2 M hydrochloric acid (10 cm^3), and then extracted with dichloromethane (30 cm^3). The organic layer was washed with 2 M hydrochloric acid (4x10 cm^3) and the aqueous layers were combined and neutralized with sodium bicarbonate. The aqueous portion was extracted with dichloromethane (4x10 cm^3), these combined organic layers washed with saturated brine (5 cm^3), dried (Na_2SO_4) and evaporated under reduced pressure to give the title compound as a yellow oil (0.46 g, 53%). IR(solution in $CHCl_3$) ν_{max} 3200br (NH), 2900, 1700 (CO), 1570, 1420, 1350 and 860 cm^{-1}; ^1H n.m.r. ($CDCl_3$) δ_H 7.23 (1 H, t, *J* 8.0 Hz, 5'-H), 6.90-6.85 (1 H, m, 6'-H), 6.83 (1 H, t, *J* 2.0 Hz, 2'-H), 6.73 (1 H, dd, *J* 8.0 and 2.0 Hz, 4'-H), 3.81 (3 H, s, $OC\underline{H}_3$), 2.68-2.56 (1 H, m, 7-H), 2.34-1.97 (2 H, m, 3-H), 2.25 (3 H, s, $NC\underline{H}_3$), 2.03 (3 H, s, 1-H), 1.86 (2

H, d, *J* 5.3 Hz, 6-H), 1.85 -1.70 (1 H, m, 4-H), 1.32 (3 H, s, 5-C$\underline{H}_3$), 1.32-1.06 (2 H, m, N$\underline{H}$ and 4-H) and 0.70 (3 H, d, *J* 6.2 Hz, 8-H); ^{13}C n.m.r. ($CDCl_3$) δ_C 208.9 (CO), 159.6 (3'-C), 148.1 (1'-C), 129.2 (Ar-$\underline{C}$H), 119.0 (Ar-$\underline{C}$H), 113.2 (Ar-$\underline{C}$H), 110.4 (Ar-$\underline{C}$H), 55.1 (O$\underline{C}H_3$), 51.9 (7-C), 51.6 (3-C), 40.1 (5-C), 38.9 ($\underline{C}H_2$), 36.8 ($\underline{C}H_2$), 33.8 and 30.0 (1-C and N$\underline{C}H_3$), 23.6 and 21.7 (5-$\underline{C}H_3$ and 8-C); MS(m/z) 277 (*M*$^+$, 2%), 259 (11), 244 (7), 206 (7), 148 (21) and 111 (37); Acc. MS(m/z) (Found: 277.2034 (*M*$^+$, 4.5%), $C_{17}H_{27}NO_2$ requires: 277.2040, -2.9 ppm).

The organic layer from the acid washing was washed with saturated aqueous sodium bicarbonate solution (5 cm^3), saturated brine (5 cm^3), dried (Na_2SO_4) and evaporated under reduced pressure to give impure starting compound (116) as a yellow oil (0.23 g, 28%).

*(5*R**, 7*R**)-5-(3-Methoxyphenyl)-5-methyl-7-[*N*-(phenylmethyl) amino]octan-2-one* (118)

Methyl lithium (1.4 M, 0.3 cm^3, 0.41 mmol) was added dropwise to a stirred solution of the benzylcaprolactam (114) (0.13 g, 0.38 mmol) in dry tetrahydrofuran (3 cm^3) at 0°C, under a nitrogen atmosphere, and the mixture was stirred at room temperature for 24 h. The reaction was poured onto ice (5 g) and then extracted with dichloromethane (4x3 cm^3). The combined organic layers were washed with saturated brine (3 cm^3), dried (Na_2SO_4) and evaporated under reduced pressure to give a brown oil. Purification by "flash" column chromatography on silica gel, eluting with ethanol/ethyl acetate (1:49) gave the title compound as a pale yellow oil (0.011 g, 8%), and the starting compound (114) as a colourless oil (0.095 g, 75%). IR(solution in $CHCl_3$) ν_{max} 3830 (NH), 2900, 2820sh, 1700 (CO), 1640, 1590sh, 1575, 1420, 1360, 1280, 1080, 1040 and 870 cm^{-1}; ^{1}H n.m.r. ($CDCl_3$) δ_H

7.31-7.17 (6 H, m, 5xPh$\underline{H}$ and 5'-H), 6.87-6.69 (3 H, m, 2'-, 4'- and 6'-H), 3.81 (3 H, s, OC$\underline{H}_3$), 3.61 (2 H, ABq, J_{AB} 12.8 Hz, PhC$\underline{H}_2$), 2.63-2.56 (1 H, m, 7-H), 2.50-2.18 (1 H, br s, N$\underline{H}$), 2.17-1.98 (1 H, m, 1x3-H), 2.03 (3 H, s, 1-H), 1.90-1.68 (1 H, m, 1x3-H), 1.78 (2 H, d, *J* 5.3 Hz, 6-H), 1.39-1.15 (2 H, m, 4-H), 1.30 (3 H, s, 5-C$\underline{H}_3$) and 0.81 (3 H, d, *J* 6.4 Hz, 8-H); MS(m/z) 353 (M^+, 2%), 348 (2, $M-CH_3$), 335 (3, $M-H_2O$), 320 (2), 310 (2, $M-CH_3CO$), 296 (3), 247 (6), 244 (4), 148 (34) and 134 (100).

*(2*R*,1'*S*)-(+)-1-(1,2-Dihydro-7-methoxy-1,4-dimethyl-1-naphthyl)*-N-*methyltrifluoroacetyl-2-propylamine* (120)

A solution of hydrogen chloride in dry dioxane (5.3 M, 10 cm^3) was added to a solution of the trifluoroacetamido ketone (81) (3.91 g, 10.5 mmol) in dry dioxane (40 cm^3) and the resulting solution heated at 70°C for 2 h, under a nitrogen atmosphere. After cooling, the solution was treated with methanol (500 cm^3) and then evaporated under reduced pressure until only 50 cm^3 remained. This process was repeated twice more. The remainder of the solvent was removed under reduced pressure to give a yellow oil. Purification by "suction flash" column chromatography on silica gel, eluting with ethyl acetate/60-80°C petroleum ether (1:19), gave the starting compound (81) as a yellow oil (1.10 g, 28%) and the title compound as a colourless crystalline solid (2.35 g, 63%). m.p. 95-96°C. $[\alpha]_D^{18°C}$ +43.9° (c 1.1 in $CHCl_3$); IR (nujol mull) ν_{max} 1685 (CO), 1610, 1570, 1490, 1420, 1310, 1240, 1230, 1190, 1130, 1090, 1070, 850, 820, 760 and 680 cm^{-1}; ^1H n.m.r. ($CDCl_3$) δ_H (1:4 mixture of rotomers) 7.15 (1 H, d, *J* 8.6 Hz, 5'-H), 6.79 (1H, d, *J* 2.6 Hz, 8'-H), 6.71 (1H, dd, *J* 8.6 and 2.6 Hz, 6'-H), 5.64-5.61 (1 H, m, 3'-H), 4.86-4.73 (1 H, m, 2-H, major

rotomer), 4.11-4.05 (1 H, m, 2-H, minor rotomer), 3.79 (3 H, s, $OC\underline{H}_3$), 2.60 (3 H, s, $NC\underline{H}_3$, minor rotomer), 2.47 (3 H, q, *J* 1.7 Hz, $NC\underline{H}_3$, major rotomer), 2.31 -1.96 (3 H, m, 2x1-H and 2'-H), 2.04 (3 H, s, 4'-$C\underline{H}_3$), 1.36 (3 H, s, 1'-$C\underline{H}_3$), 1.26 (1 H, dd, *J* 15.1 and 2.6 Hz, 2'-H), 1.12 (3 H, d, *J* 6.4 Hz, 3-H, minor rotomer) and 1.04 (3 H, d, *J* 7.0 Hz, 3-H, major rotomer); MS(m/z) 355 (M^+, 35%), 188 (100), 187 (94), 186 (71) and 172 (47); Analysis (Found: C, 64.5; H, 6.91; N, 3.93, $C_{19}H_{24}F_3NO_2$ requires: C, 64.2; H, 6.82; N, 3.94%).

Crystal Data.-$C_{19}H_{24}F_3NO_2$, *M* = 355.44. Orthorhombic, *a* = 8.992 (3), *b* = 13.042 (3), *c* = 15.511 (5) Å, *V* = 1819.0 Å^3 (by least squares refinement on diffractometer angles for 12 automatically centred reflections, λ = 0.71069 Å), space group $P2_12_12_1$, *Z* = 4, D_X = 1.30 g cm^{-3}. Colourless slabs. Crystal dimensions: 0.30 x 0.30 x 0.33 mm, μ(Mo-K_α) = 0.64 cm^{-1}.

Data Collection and Processing.[62]-Hilger and Watts Y290 4-circle diffractometer, graphite monochromated Mo-K_α radiation; 1624 reflections were measured ($2 \leq \Theta \leq 24°$), 895 were unique with $I < 3 < \sigma(I)$. No crystal decay was detected during data collection.

Structure Analysis and Refinement.-Direct methods[63] were successful in locating all non-hydrogen atoms. The structure was refined using SHELX*76*.[64] The weighting scheme $w = 8.1764\ [\sigma^2(F_o) + 0.08\ F_o^2]$, with $\sigma(F_o)$ from counting statistics[65,66,67] gave satisfactory agreement analyses. Final *R* and R_w values were 0.0925. Sources of scattering factor data are given in refs. 65-67.

*(2*R*,*1'*R*)*-1-(1,2-Dihydro-7-methoxy-1,4-dimethyl-1-naphthyl)*-N-*methyl-2-propylamine* (119)

Concentrated hydrochloric acid (0.3 cm^3) was added dropwise to

a solution of the aminoketone (117) (0.23 g, 0.83 mmol) and the solution was heated at 70°C for 6 h, under a nitrogen atmosphere. After cooling, water (20 cm^3) was added and the solution was basified with 2 M aqueous sodium hydroxide solution. The mixture was extracted with dichloromethane (4x10 cm^3) and the combined organic portions were washed with saturated brine (5 cm^3), dried (Na_2SO_4) and evaporated under reduced pressure to give a yellow oil. Purification by "flash" column chromatography on silica gel, eluting with dichloromethane/ethanol/aqueous ammonia (90:8:1), gave the title compound as a colourless oil (0.13 g, 61%). IR(solution in $CHCl_3$) ν_{max} 3300br w (NH), 2900, 2840sh, 1710w, 1600, 1570sh, 1480, 1450, 1370, 1290 and 1050 cm^{-1}; ^1H n.m.r. ($CDCl_3$) δ_H 7.18 (1 H, d, *J* 8.5 Hz, 5'-H), 6.87 (1 H, d, *J* 2.7 Hz, 8'-H), 6.71 (1 H, dd, *J* 8.5 and 2.7 Hz, 6'-H), 5.62 (1 H, m, 3'-H), 3.81 (3 H, s, $OC\underline{H}_3$), 2.47 (1 H, m, 1-H), 2.29 (3 H, s, $NC\underline{H}_3$), 2.26-2.17 (2 H, m, 2'-H), 2.02 (3 H, d, *J* 1.1 Hz, 4'-$C\underline{H}_3$), 1.55 (2 H, ABX, J_{AB} 14.2 Hz, $J_{AX,BX}$ 4.9 Hz, 1-H), 1.35 (3 H, s, 2-$C\underline{H}_3$), 1.17 (1 H, br s, N<u>H</u>) and 0.74 (3 H, d, *J* 6.2 Hz, 3-H); ^{13}C n.m.r. ($CDCl_3$) δ_C 124.3, 121.3, 111.9 and 109.8 (3'-, 5'-, 6'- and 8'-C), 55.2 ($OC\underline{H}_3$), 52.1 (2-C), 47.4 ($\underline{C}H_2$), 36.8 ($\underline{C}H_2$), 33.9 ($NC\underline{H}_3$), 29.7 (1'-C), 26.9 (4'-$\underline{C}H_3$), 22.2 and 19.4 (3-C and 1'-$\underline{C}H_3$); MS(m/z) 259 (*M*+, 8%), 213 (5), 188 (48), 186 (40) and 173 (31); Acc. MS(m/z) (Found: 259.1933 (*M*+, 12%), $C_{17}H_{25}NO$ requires: 259.1934, -1.2 ppm).

*(2*R*,*1'*R*)-1-(1,2-Dihydro-7-methoxy-1,4-dimethyl-1-naphthyl)-N-methyl-2-propylamine* (119)

A mixture of the aminoketone (117) (0.050 g, 0.18 mmol) and polyphosphoric acid (0.3 g) were heated at 120°C for 5 min, under a nitrogen atmosphere. After cooling, cold 2 M aqueous sodium

hydroxide solution (5 cm^3) was added slowly and the mixture extracted with dichloromethane (4x3 cm^3). The combined organic layers were washed with saturated brine (3 cm^3), dried (Na_2SO_4) and evaporated under reduced pressure to give a yellow oil (0.047 g). Purification by "flash" column chromatography on silica gel, eluting with dichloromethane/ethanol/aqueous ammonia (200:8:1), gave the title compound as a colourless oil (0.005 g, 10%) and the starting compound (119) as a pale yellow oil (0.020 g, 40%). The spectral details were identical with those described previously for this compound (p.92).

*(2*R,*1'*S*)-(+)-1-(1,2-Dihydro-7-methoxy-1,4-dimethyl-1-naphthyl)*-N-*methyl-2-propylamine* (132)

A mixture of the trifluoroacetamido dihydronaphthalene (120) (0.50 g, 1.41 mmol) and anhydrous potassium bicarbonate (1.0 g, 7.24 mmol) in 80% methanol (5 cm^3) was treated with ultrasound in an ultrasonic bath for 18 h, under a nitrogen atmosphere. The resulting solution was poured into water (10 cm^3) and extracted with ethyl acetate (4x10 cm^3). The combined organic layers were washed with saturated brine (5 cm^3), dried (Na_2SO_4) and evaporated under reduced pressure to give the pure title compound as a pale yellow oil (0.36 g, 99%). $[\alpha]_D^{18°C}$ +40.8° (c 1.4 in CH_2Cl_2); IR(neat) ν_{max} 3360w (NH), 3040sh, 2970, 2940sh, 2840, 2790, 1685w, 1610, 1570, 1490, 1460, 1420, 1380, 1310, 1230, 1070, 1040 and 840 cm^{-1}; ^1H n.m.r. ($CDCl_3$) δ_H 7.19 (1 H, d, *J* 8.4 Hz, 5'-H), 6.89 (1 H, d, *J* 2.6 Hz, 8'-H), 6.73 (1 H, dd, *J* 8.4 and 2.6 Hz, 6'-H), 5.65-5.58 (1 H, m, 3'-H), 3.82 (3 H, s, $OC\underline{H}_3$), 2.43 (1 H, pd, *J* 6.4 and 3.3 Hz, 2-H), 2.32-2.23 (1 H, m, 2'-H), 2.12-2.02 (1 H, m, 2'-H), 2.03 (3 H, m, 4'-$C\underline{H}_3$), 1.99 (3 H, s, $NC\underline{H}_3$), 1.94 (1 H, dd, *J* 14.4 and 6.4 Hz, 1-H), 1.33 (3 H, s, 1'-$C\underline{H}_3$), 1.25 (2 H, br s

and dd, *J* 14.4 and 3.3 Hz, N<u>H</u> and 1-H) and 0.98 (3 H, d, *J* 6.4 Hz, 3-H).

η^6-cis/trans-*[(2*R**,1′R*)-1-(1,2-Dihydro-7-methoxy-1,4-dimethyl-1-naphthyl)*-N-*methyl-2-propylamine]chromium tricarbonyl* (129) and (128)

Chromium hexacarbonyl (0.12 g, 0.55 mmol) and the amino dihydronaphthalene (119) (0.13 g, 0.50 mmol) were placed in a round bottomed flask (5 cm^3) fitted with a water condenser and a nitrogen/vacuum system. After the system had been thoroughly flushed out with nitrogen, a degassed solution of di-*n*-butyl ether (3 cm^3) and tetrahydrofuran (0.3 cm^3) was added *via* cannula and the mixture was heated under reflux for 30 h. (The solution had changed colour from orange to black in this time.) The solution was allowed to cool before being filtered through an alumina pad which had been previously flushed with nitrogen. A degassed solution of dichloromethane/ethanol/triethylamine (90:8:1) was used to wash the filter pad, and the combined filtrates were evaporated under reduced pressure to give an orange oil. Purification by "flash" column chromatography on silica gel (which had been flushed with nitrogen prior to use), eluting with a degassed solution of dichloromethane/ethanol/triethylamine (180:8:1) gave the title compound as an orange oil (0.048 g, 24%), which was sensitive to both air and light. ^{1}H n.m.r. ($CDCl_3$) δ_H (2:1 mixture of two stereomers) 5.69–5.12 (4 H, m, 3'-, 5'-, 6'- and 8'-H), 3.72 (3 H, s, O<u>C</u>H$_3$), 2.68–2.39 (2 H, m), 2.36–2.20 (1 H, m), 2.28 major and 2.17 minor (3 H, 2xs, N<u>C</u>H$_3$), 1.88 (3 H, s, 4'-<u>C</u>H$_3$), 1.68–1.09 (3 H, m), 1.47 major and 1.16 minor (3 H, 2xs, 1'-<u>C</u>H$_3$) and 0.90 minor and 0.72 major (3 H, 2xd, *J* 6 Hz, 3-H).

η^6-cis/trans-*[(2R,1'S)-1-(1,2-Dihydro-7-methoxy-1,4-dimethyl-1-naphthyl)*-N-*methyltrifluoroacetyl-2-propyl-amine]chromium tricarbonyl* (130) and (82)

Chromium hexacarbonyl (0.68 g, 3.09 mmol) and the trifluoro-acetamido dihydronaphthalene (120) (1.00 g, 2.81 mmol) were placed in a round bottomed flask (50 cm^3) fitted with a water condenser and a nitrogen/vacuum system. After the system had been thoroughly flushed out with nitrogen, a degassed solution of di-*n*-butyl ether (18 cm^3) and tetrahydrofuran (2 cm^3) was added *via* cannula and the mixture was heated under reflux for 40 h. (The solution had changed colour from orange to green in this time.) The solution was allowed to cool before being filtered through an alumina pad which had been previously flushed with nitrogen. A degassed solution of 60-80°C petroleum ether and then ethyl acetate was used to wash the filter pad, and the filtrate was evaporated under reduced pressure to give an orange oil. Purification by "flash" column chromatography on silica gel (which had been flushed with nitrogen prior to use), eluting with a gradient of degassed ethyl acetate/60-80°C petroleum ether (3:22 to 3:17 to 1:4) gave the *trans*-title (82) compound as a yellow/orange microcrystalline solid (0.49 g, 36%) m.p. 95-96°C, the *cis*-title compound (130) as an orange waxy solid (0.05 g, 4%) m.p. 105-106°C and the starting compound (120) as a pale yellow crystalline solid (0.58 g, 58%). *Trans*-complex: IR(nujol mull) ν_{max} 1960, 1950, 1890 and 1850 (Cr-CO), 1680 (amide CO), 1540, 1280, 1240, 1190, 1150, 1090, 1020 and 670 cm^{-1}; ^1H n.m.r. ($CDCl_3$) δ_H 5.66 (1 H, d, *J* 6 Hz, 3'-H), 5.58 (1 H, d, *J* 7 Hz, 5'-H), 5.19-5.14 (2 H, m, 6'- and 8'-H), 4.82 (1 H, br p, *J* 7 Hz, 2-H), 3.70 (3 H, s, $OC\underline{H}_3$), 2.63 (4 H, m and s, $NC\underline{H}_3$ and 1x2'-H), 2.24 (1 H, dd, *J* 14 and 9 Hz, 1x1-H), 2.09 (1 H, dd, *J* 17 and 7 Hz,

2.24 (1 H, dd, *J* 14 and 9 Hz, 1x1-H), 2.09 (1 H, dd, *J* 17 and 7 Hz, 1x2'-H), 1.92 (3 H, s, 4'-C$\underline{H}_3$), 1.44 (3 H, s, 1'-C$\underline{H}_3$), 1.28 (1 H, d, *J* 14 Hz, 1x1-H) and 1.08 (3 H, d, *J* 7 Hz, 3-H); ^{13}C n.m.r. ($CDCl_3$) δ_C 233.3 (Cr-CO), 140.7 (4'-C), 128.2 (7'-C), 125.0 (3'-C), 117.7 and 97.2 (4'a- and 8'a-C), 90.0, 77.6 and 76.9 (5'-, 6'- and 8'-C), 55.3 (O$\underline{C}H_3$), 47.0 (2-C), 41.1 and 37.4 (2'- and 1-C), 35.9 (1'-C), 32.4 (N$\underline{C}H_3$), 23.7, 20.0 and 18.7 (3x$\underline{C}H_3$); MS(m/z, CI) 492 (*M*+1, 18%), 491 (23, *M*$^+$), 407 (16, *M*-3xCO), 356 (100), 355 (48, *M*-$Cr(CO)_3$), 188 (43), 187 (52) and 186 (49); Analysis (Found: C, 53.9; H, 5.05; N, 2.84, $C_{22}H_{24}CrF_3NO_5$ requires: C, 53.8; H, 4.93; N, 2.85%). *Cis*-complex: IR(nujol mull) ν_{max} 1970, 1940, 1890, 1860 and 1840sh (Cr-CO), 1690 (amide CO), 1540, 1380, 1280, 1240, 1180, 1140, 1100, 1020, 750, 710 and 670 cm^{-1}; ^{1}H n.m.r. ($CDCl_3$) δ_H 5.69-5.59 (2 H, m, 3'- and 5'-H), 5.17-5.04 (3 H, m, 2-, 6'- and 8'-H), 3.72 (3 H, s, O$\underline{C}H_3$), 3.05 (3 H, s, N$\underline{C}H_3$), 2.59-2.02 (3 H, m, 2x2'-H and 1x1-H), 1.88 (3 H, s, 4'-C$\underline{H}_3$), 1.31 (3 H, d, *J* 7 Hz, 3-H) and 1.17-1.02 (4 H, m and s, 1x1-H and 1'-C$\underline{H}_3$); ^{13}C n.m.r. ($CDCl_3$) δ_C 233.5 (Cr-CO), 141.7 (4'-C), 127.3 (7'-C), 125.0 (3'-C), 118.6 and 97.3 (4'a- and 8'a-C), 90.5, 77.2 and 75.0 (5'-, 6'- and 8'-C), 55.7 (O$\underline{C}H_3$), 47.1 (2-C), 41.6 and 33.9 (2'- and 1-C), 35.4 (1'-C), 26.5, 20.4 and 18.8 (3x$\underline{C}H_3$); MS(m/z) 407 (*M*-3xCO, 18%), 355 (41, *M*-$Cr(CO)_3$), 213 (11), 201 (13), 188 (85), 187 (100) and 186 (93); Acc. MS(m/z) (Found for fragment: 407.1180 (*M*-3xCO, 22%), $C_{19}H_{24}CrF_3NO_2$ requires: 407.1158, +5.4 ppm).

*(1*R,*2*S,*4*R,*6*R*)-(-)-1,2,3,4,5,6-Hexahydro-8-methoxy-1,3,4,6-tetramethyl-2,6-methano-3-benzazocine* (83)

Degassed aqueous methanol (67%, 6 cm^3) was added *via* cannula to a mixture of η^6-*trans*-trifluoroacetamidodihydronaphthalene

chromium tricarbonyl complex (82) (0.10 g, 0.2 mmol) and anhydrous potassium carbonate (0.20 g, 1.4 mmol) under an argon atmosphere. The mixture was treated with ultrasound in an ultrasonic bath for 72 h, during which time the potassium carbonate went into solution. At the end of this period three components were visible by t.l.c.: the starting material (82); the amino derivative of the starting material (135), and the chromium tricarbonyl complex of the title compound (133). The solution was added to water (5 cm^3) and extracted with ethyl acetate (4x5 cm^3). The combined organic portions were washed with brine (3 cm^3) and quickly dried (Na_2SO_4) and evaporated under reduced pressure to give an orange oil (0.08 g). This residue was then dissolved in (5 cm^3) and placed in a sunlit position, in the presence of air, for 24 h. (After this time the orange solution had changed into a green suspension.) The suspension was evaporated under reduced pressure and the residue then purified by "flash" column chromatography on silica gel, eluting with dichloromethane/ethanol/aqueous ammonia (100:8:1) to give a mixture of the title compound and the aminodihydronaphthalene (132). Further purification by preparative t.l.c. on silica gel (1 mm, 60 GF254 Merck), using the same eluant as before, gave the the aminodihydronaphthalene (132) (0.030 g, 57%) and the pure title compound as a white waxy solid (0.009 g, 17% overall yield, 40% based on recovered aminodihydronaphthalene, 88). m.p. 66-67°C. $[\alpha]_D^{18°C}$ -59.3° (c 2.0 in CH_2Cl_2); IR(solution in $CHCl_3$) ν_{max} 2980, 2920sh, 2900sh, 2500w, 1600, 1570, 1480, 1450, 1420sh, 1370, 1300, 1280, 1160, 1100, 1090, 1040, 1010, 900 and 860 cm^{-1}; ^1H n.m.r. ($CDCl_3$) δ_H 7.08 (1 H, d, *J* 8.4 Hz, 10-H), 6.80 (1 H, d, *J* 2.7 Hz, 7-H), 6.73 (1 H, dd, *J* 8.4 and 2.7 Hz, 9-H), 3.79 (3 H, s, $OC\underline{H}_3$), 3.12 (1 H, q, *J* 7.1 Hz, 1-H), 2.88 (1 H, t, *J* 3.1 Hz,

2-H), 2.42 (3 H, s, $NC\underline{H}_3$), 2.13-1.92 (2 H, m, 1x4- and 1x11-H), 1.69 (1 H, ddd, *J* 12.6, 3.8 and 1.1 Hz, 1x11-H), 1.35 (5 H, s and m, 6-$C\underline{H}_3$ and 5-H), 1.22 (3 H, *J* 7.1 Hz, 1-$C\underline{H}_3$) and 0.92 (3 H, d, *J* 6.2 Hz, 4-$C\underline{H}_3$); ^{13}C n.m.r. ($CDCl_3$) δ_C 157.7 (8-C), 145.4 and 145.6 (6a- and 10a-C), 128.9, 111.2 and 110.1 (7-, 9- and 10-C), 62.8 ($\underline{C}H$), 55.1 ($O\underline{C}H_3$), 50.1 ($\underline{C}H$ and $\underline{C}H_2$), 39.7 (NCH_3), 36.0 ($\underline{C}H_2$), 33.8 (6-C), 29.6 (1-C), 28.0, 24.9 and 20.6 ($3x\underline{C}H_3$); MS(m/z) 259 (*M*$^+$, 20%), 244 (100, *M*-CH_3), 187 (16) and 124 (31); Acc. MS(m/z) (Found: 259.1936 (*M*$^+$, 26%), $C_{17}H_{25}NO$ requires: 259.1934, +0.8 ppm); Enantiomeric excess 86% (±2%, determined by ^1H n.m.r. in $CDCl_3$ using 0.050g TFAE and 0.007g sample, splitting observed in doublet at 0.9 ppm).

Attempted synthesis of (2S,4S*,6R*)-1,2,3,4,5,6-hexahydro-8-methoxy-1,3,4,6-tetramethyl-2,6-methano-3-benzazocine* (136)

The amino chromium complex (123) (0.043 g, 0.11 mmol) was placed in a round bottomed flask (5 cm^3), fitted with a nitrogen/vacuum system, and the system was thoroughly flushed out with nitrogen. A degassed solution of dry ether (2 cm^3) was added *via* cannula and the solution cooled to 0°C. A degassed solution of *t*-butyl lithium (1.87 M, 0.06 cm^3, 0.11 mmol) was added, again *via* cannula, to the stirred solution at 0°C. After stirring at 0°C for 15 min, the solution was cooled to -78°C and a degassed aqueous solution of ammonium chloride (1 cm^3) was added *via* cannula. The solution was allowed to warm to room temperature over the period of 1 h. No higher running product was visible by t.l.c. After a normal work up procedure only starting material was recovered.

Attempted synthesis of η^6-trans-*[(1*R,*2*S,*4*R,*6*R*)*-1,2,3,4,5,6-hexahydro-8-methoxy-1,3,4,6-tetramethyl-1-methylthio-2,6-methano-3-benzazocine]chromium tricarbonyl* (137)

The trifluoroacetamido chromium complex (123) (0.20 g, 0.41 mmol) was placed in a round bottomed flask (10 cm^3), fitted with a nitrogen/vacuum system, and the system was thoroughly flushed out with nitrogen. A degassed solution of dry ether (5 cm^3) was added *via* cannula and the solution cooled to -78°C. A degassed solution of methyl lithium (1.4 M, 0.48 cm^3, 0.66 mmol) was added, again *via* cannula, to the stirred solution at -78°C. After stirring at -78°C for 2 h, a degassed solution of dimethyl disulphide (0.11 cm^3, 0.12 g, 1.23 mmol) in dry ether (1 cm^3) was added *via* cannula, at -78°C. The solution was stirred at -78°C, under a nitrogen atmosphere, for 10 h and then allowed to warm to room temperature over the period of 1 h. Water (5 cm^3) was added and the mixture was extracted with ethyl acetate (4x5 cm^3). The combined organic layers were washed with saturated brine (5 cm^3), dried (Na_2SO_4) and evaporated under reduced pressure to give an orange oil. Purification by "flash" column chromatography on silica gel, eluting with a degassed solution of dichloromethane/ethanol/triethylamine (250:8:1), gave the starting compound (102) (0.080 g, 40%), the amino chromium complex (135) (0.050 g, 31%) and the acetamido chromium complex (131) (0.015 g, 8%) as orange oils. The acetamido chromium complex (131) was dissolved in ether (3 cm^3) and stood in a sunlit position in the presence of air, for 24 h, until the solution had changed colour from yellow to dark green. The solution was evaporated under reduced pressure and then purified by "flash" column chromatography on silica gel, eluting with dichloromethane/ethanol/aqueous ammonia (100:8:1), to give the

acetamido dihydronaphthalene (138) as a colourless oil (0.007 g, 5%). $[\alpha]_D^{18°C}$ +41.1° (c 1.1 in CH_2Cl_2); IR(solution in $CHCl_3$) ν_{max} 2980, 2820sh, 1650 (CO), 1600, 1570, 1490, 1420, 1310, 1240, 1080, 1040, 850, 820 and 760 cm^{-1}; ^1H n.m.r. ($CDCl_3$) δ_H (3:1 mixture of rotomers, major rotomer) 7.14 (1 H, *J* 8.4 Hz, 5-H), 6.83 (1 H, d, *J* 2.6 Hz, 8-H), 6.70 (1 H, dd, *J* 8.4 and 2.6 Hz, 6-H), 5.67-5.58 (1 H, m, 3-H), 5.04-4.91 (1 H, m, 1'-H), 3.83 (3 H, s, $OC\underline{H}_3$), 2.18 (3 H, s, $NC\underline{H}_3$), 2.32-2.07 (2 H, m, 2- and/or 2'-H), 2.04 (3 H, m, 4-$C\underline{H}_3$), 1.77 (3 H, s, $COC\underline{H}_3$), 1.46-1.10 (2 H, m, 2- and/or 2'-H), 1.37 (3 H, s, 1-$C\underline{H}_3$) and 0.93 (3 H, d, *J* 7.2 Hz, 1'-$C\underline{H}_3$); MS(m/z) 301 (*M*+, 16%), 223 (11), 186 (72), 115 (100); Acc. MS(m/z) (Found: 301.2039 (*M*+, 24%), $C_{19}H_{27}NO_2$ requires: 301.2039).

Amino complex: IR(neat) ν_{max} 3350br w (NH or H_2O), 2960, 2940, 2720 (NH^+), 2460 (NH^+), 1950 and 1860 (Cr-CO), 1600, 1540, 1460, 1440sh, 1380, 1280, 1230, 1060, 1020, 910, 840, 730 and 670 cm^{-1}; ^1H n.m.r. ($CDCl_3$) δ_H 5.62-5.56 (2 H, m, 3- and 5-H), 5.30-5.14 (2 H, m, 6- and 8-H), 3.73 (3 H, s, $OC\underline{H}_3$), 2.97-2.48 (2 H, m), 2.30 (3 H, s, $NC\underline{H}_3$), 2.20-1.96 (1 H, m), 1.90 (3 H, s, 4-$C\underline{H}_3$), 1.60-1.04 (2 H, m), 1.56 (3 H, s, 1-$C\underline{H}_3$) and 1.17 (3 H, s, 1'-$C\underline{H}_3$); ^{13}C n.m.r. ($CDCl_3$) δ_C 233.6 (Cr-CO), 141.4 (4-C), 128.4 (7-C), 77.7 and 76.4 (5-, 6- and 8-C), 55.8 ($O\underline{C}H_3$), 52.0 (1'-C), 32.4 ($N\underline{C}H_3$), 24.7, 21.2 and 18.9 (3x$\underline{C}H_3$); MS(m/z) 395 (*M*+, 8%), 311 (31, *M*-3xCO), 259 (7, *M*-$Cr(CO)_3$), 238 (59), 188 (28) and 186 (49); Acc. MS(m/z) (Found: 395.1171 (*M*+, 19%), $C_{20}H_{25}CrNO_4$ requires: 395.1182, -2.8 ppm).

REFERENCES

REFERENCES

1. a) J.M. Gulland and R. Robinson, *J. Chem. Soc.*, 1923, 980.
   b) J.M. Gulland and R. Robinson, *Mem. Proc. Manchester Lit. Phil. Soc.*, 1925, 69, 79.
2. C. Schöpf, *Liebigs Ann. Chem.*, 1927, 452, 211.
3. a) W.R. Martin, C.G. Eades, J.A. Thompson, R.E. Huppler and P.E. Gilbert, *J. Pharmacol. Exp. Ther.*, 1976, 197, 517.
   b) W.R. Martin and P.E. Gilbert, *J. Pharmacol. Exp. Ther.*, 1976, 198, 66.
   c) W.R. Martin and E.T. Iwamoto, *Med. Res. Rev.*, 1981, 1, 441.
4. H.W. Kosterlitz, J.A.H. Lord, A.A. Waterfield and J. Hughes, *Nature (London)*, 1977, 267, 495.
5. a) H.W. Kosterlitz and A.A. Waterfield, *Ann. Rev. Pharmacol.*, 1975, 15, 29.
   b) A.F. Casy and R.T. Parfitt, "Opioid Analgesics: Chemistry and Receptors", Plenum Press, New York, London, 1986.
6. J.A. Barltrop, *J. Chem. Soc.*, 1947, 399.
7. E.L. May, J.H. Ager and J.G. Murphy, *J. Org. Chem.*, 1960, 25, 1386.
8. a) R. Grewe and A. Mondon, *Chem. Ber.*, 1948, 81, 279.
   b) R. Grewe, A. Mondon and E. Nolte, *Liebigs Ann. Chem.*, 1949, 564, 161.
9. a) M. Takeda, H. Inoue, S. Saito and H. Kugita, *J. Org. Chem.* 1972, 37, 2677.
   b) G. Kavadias, S. Velkof and B. Belleau, *Can. J. Chem.*, 1979, 57, 1852 and 1856.

10. E.L. May and J.G. Murphy, *J. Org. Chem.*, 1955, 20, 257.

11. Neth. P. Appl. 6,606,057/1966, *Chem. Abstr.*, 1967, 67, 21854e.

12. E.L. May and E.M. Fry, *J. Org. Chem.*, 1957, 22, 1366.

13. E.M. Fry, *J. Org. Chem.*, 1963, 28, 1869.

14. N. Yokoyama, F.B. Block and F.H. Clarke, *J. Med. Chem.*, 1970, 13, 488.

15. E.L. May and E.M. Fry, *J. Org. Chem.*, 1961, 26, 2592.

16. E.L. May and H. Inoue, *J. Med. Chem.*, 1976, 19, 259.

17. T. Kametani, M. Nishimura, Y. Suzuki and T. Honda, *Heterocycles*, 1986, 24, 1791.

18. a) T. Kametani, Y. Suzuki and T. Honda, *J. Chem. Soc. Perkin Trans. I*, 1986, 1373.
b) J.M. Surzur, L. Stella and B. Raynier, *Tetrahedron*, 1981, 37, 2843.

19. M.A. Tius and A. Thurkauf, *Tetrahedron Lett.*, 1986, 27, 4541.

20. C.A. Broka and J.F. Gerlits, *J. Org. Chem.*, 1988, 53, 2144.

21. a) A.I. Meyers and T.R. Bailey, *J. Org. Chem.*, 1986, 51, 872.
b) A.I. Meyers, D.A. Dickman and T.R. Bailey, *J. Am. Chem. Soc.*, 1985, 107, 7974.

22. R. Noyori, H. Takaya, Y. Hsiao and M. Kitamura, *Tetrahedron Lett.*, 1987, 28, 4829.

23. H. Sdassi, G. Revial, M. Pfau and J. d'Angelo, *Tetrahedron Lett.*, 1990, 31, 875.

24. B.P. 1563745/1977.

25. a) A.O. Ogundaini and R.T. Parfitt, *J. Med. Chem.*, 1985, 28, 177.
b) R.T. Parfitt and S.M. Walters, *J. Med. Chem.*, 1971, 14, 565.

c)A. Ogundaini and R.T. Parfitt, *J. Chem. Res.*, 1983, (*S*) 135 and (*M*) 1351.

d) B.P. 1261481/1970.

e) B.P. 1261693/1970.

26. a) D. Enders, "Asymmetric Synthesis", Ed. J.R. Morrison, Academic Press, New York, 1984, Vol. 3, Chapt. 4.

b) D. Enders, P. Fey and H. Kipphardt, *Org. Synth.*, 1987, 65, 183.

27. a) F.G. Bordwell, R.G. Scamehorn, R.R. Frame, J.G. Strong and S. Meyerson, *J. Am. Chem. Soc.*, 1967, 89, 6704.

b) R.L.N. Harris, F. Komitsky and C. Djerassi, *J. Am. Chem. Soc.*, 1967, 89, 4765.

28. a) F. Nerdel and H. Frohlich, *Chem. Ber.*, 1952, 85, 171.

b) H. Ahlbrecht, W. Funk and M.T. Reiner, *Tetrahedron*, 1976, 32, 479.

29. E.J. Corey and M. Chaykovsky, *J. Am. Chem. Soc.*, 1965, 87, 1353.

30. a) A.I. Meyers and M.A. Sturgess, *Tetrahedron Lett.*, 1988, 29, 5339.

b) A.I. Meyers, G.S. Poindexter and Z. Brich, *J. Org. Chem.*, 1978, 43, 892.

c) T. Sone, S. Terashima and S-I Yamada, *Chem. Pharm. Bull.*, 1976, 24, 1273.

d) J.K. Whitesell and M.A. Whitesell, *J. Org. Chem.*, 1977, 42, 377.

e) S.J. Barer, W.B. Schweizer and D. Seebach, *Helv. Chim. Acta*, 1982, 65, 1637.

31. R.E. Gawley, E.J. Termine and J. Aube, *Tetrahedron Lett.*,

1980, 21, 3115.

32. H. Lio, M. Monden, K. Okada and T. Tokoroyama, *J. Chem. Soc. Chem. Commun.*, 1987, 358.

33. H. Eichenauer, Ph.D. Dissertation, Justus-Liebig-Univ., Giessen, 1980.

34. W.C. Hamilton and J.C. Ibers, "Hydrogen Bonding in Solids", W.A Benjamin, New York, 1968, p.16.

35. a) C. Perez and F. Fernandez, *J. Chem. Res.*, 1987, (*S*) 340.
b) C. Perez and F. Fernandez, *Heterocycles*, 1987, 26, 2411.

36. a) J. Schmidt-Thome, *Chem. Ber.*, 1955, 895.
b) H. Dannenberg and T. Kohler, *Chem. Ber.*, 1964, 97, 140.

37. G.A. Olah and A.P. Fung, *Synthesis*, 1979, 537.

38. K. Oka and S. Hara, *J. Org. Chem.*, 1978, 43, 3790.

39. B.C. Challis and J.A. Challis, "The Chemistry of Amides", Ed. J. Zabicky, Interscience, London, 1970, p. 748.

40. a) G.C. Hopkins, J.P. Jonak, H.J. Minnemeyer and H. Tieckelmann, *J. Org. Chem.*, 1967, 32, 4040.
b) M. Julia and H. Mestdagh, *Tetrahedron*, 39, 1983, 443 and references therein.

41. H.K. Hall Jr., *J. Am. Chem. Soc.*, 1956, 78, 2717.

42. B.C. Challis and J.A. Challis, "The Chemistry of Amides", Ed. J. Zabicky, Interscience, London, 1970, p. 761.

43. a) R. Lukes and A. Fabryova, *Collect. Czech. Chem. Commun.*, 1960, 25, 1618.
b) R. Lukes, V. Dudek, O. Sedlakova and J. Koran, *Collect. Czech. Chem. Commun.*, 1961, 26, 1105.

44. A.I. Meyers and P. Beak, *Acc. Chem. Res.*, 1986, 19, 356.

45. T.S. Chen, P. Canonne and L.C. Leitch, *Synthesis*, 1973, 620.

46. A.J. Birch, A.H. Jackson and P.V.R. Shannon,
J. Chem. Soc. Perkin Trans. I, 1974, 2185.

47. G.R. Knox, D.G. Leppard, P.L. Pauson and W.E. Watts,
J. Organomet. Chem., 1972, 34, 347.

48. M.F. Semmelhack, W. Seufert and L. Keller,
J. Am. Chem. Soc., 1980, 102, 6584.

49. M. Uemura, K. Take, K. Isobe, T. Minami and Y. Hayashi,
Tetrahedron, 1985, 41, 5771.

50. a) D.W. Clack and L.A.P. Kane-Maguire,
J. Organomet. Chem., 1978, 145, 201.
b) J. Brocard, A. Laconi, D. Couturier, S. Top and G. Jaouen,
J. Am. Chem. Soc., 1984, 106, 2207.

51. a) S.G. Davies, J. Blagg and B.E. Mobbs,
J. Chem. Soc. Perkin Trans. I, 1986, 2257.
b) H. des Abbayes and M.A. Boudeville, *J. Org. Chem.*,
1977, 42, 4104.

52. I.U. Khand, C.A.L. Mahaffy and P.L. Pauson,
J. Chem. Res., 1978, (*S*) 352, (*M*) 4454 and refs. therein.

53. M.D. Rausch, G.A. Moser, E.J. Zaiko and A.L. Lipman,
J. Organomet. Chem., 1970, 23, 185.

54. a) C.A.L. Mahaffy and P.L. Pauson, *Inorg. Synth.*,
1979, 19, 154.
b) J. Vebrel and R. Mercier, *J. Organomet. Chem.*,
1982, 235, 197 and refs. therein.

55. S.G. Davies and C.L. Goodfellow, *J. Organomet. Chem.*,
1988, 340, 195.

56. a) D.E.F. Gracey, W.R. Jackson, W.B. Jenning and

T.R.B. Mitchell, *J. Chem. Soc. B*, 1969, 1204.

b) J. Besancon, S. Top, J. Tirouflet, B. Gautheron and Y. Dusausoy, *J. Organomet. Chem.*, 1975, 94, 35.

c) M. Uemura, T. Kobayashi, T. Minami and Y. Hayashi, *J. Org. Chem.*, 1986, 51, 2589.

57. a) S.G. Davies, J. Blagg, N.J. Holman, C.A. Laughton and B.E. Mobbs, *J. Chem. Soc. Perkin Trans. I*, 1986, 1581.

b) M. Uemura, K. Isobe, K. Take and Y. Hayashi, *J. Org. Chem.*, 1983, 48, 3855.

c) A. Meyer and O. Hofer, *J. Am. Chem. Soc.*, 1980, 102, 4410.

58. S.K. Hirani and R.T. Parfitt, *J. Heterocycl. Chem.*, 1987, 24, 489.

59. A. Ogundaini and R.T. Parfitt, *J. Chem. Res.*, 1983, (*S*) 135, (*M*) 1351.

60. Y.K. Sawa and J. Irisawa, *Tetrahedron*, 1965, 21, 1129.

61. a) S.G. Davies, J. Blagg, S.J. Coote, D. Middlemiss and A. Naylor, *J. Chem. Soc. Perkin Trans. I*, 1987, 689.

b) H.B. Arzeno, D.H.R. Barton, S.G. Davies, X. Lusinchi, B. Meunier and C. Pascard, *Nouv. J. Chim.*, 1980, 4, 369.

c) S.G. Davies and J. Blagg, *J. Chem. Soc. Chem. Commun.*, 1986, 492.

62. K.C. Molloy, P.C. Waterfield and M.F. Mahon, *J. Organomet. Chem.*, 1989, 365, 61.

63. G.M. Sheldrick, SHELX86 computer program for crystal structure determination, University of Göttingen 1986.

64. G.M. Sheldrick. SHELX76 computer program for crystal structure determination, University of Cambridge 1976.

65. D.T. Cromer and J.B. Mann, *Acta Crystallogr., Sect. A*, 1968, A24, 321.

66. R.F. Stewart, E.R. Davidson and W.T. Simpson, *J. Phys. Chem.*, 1965, 42, 3175.

67. D.T. Cromer and D.J. Liberman, *J. Phys. Chem.*, 1970, 53, 1891.

68. a) "Flash" column chromatography: W.C. Still, M. Kahn and A. Mitra, *J. Org. Chem.*, 1978, 43, 2923.
b) "Suction flash" column chromatography: L.M. Harwood, Unpublished Memorandum, University of Manchester, 1982.

APPENDIX A-

X-RAY CRYSTALLOGRAPHIC DATA

Table 3

X-Ray Crystallographic Data of (2*R*-cis, *E*)-(+)-4-(3-Methoxyphenyl)-2,4-dimethylcyclohexanone oxime (101)

Bond Lengths (Å)

O1-N1	1.433 (4)	N1-C1	1.276 (5)
C1-C2	1.504 (6)	C1-C6	1.511 (5)
C2-C3	1.526 (6)	C3-C4	1.549 (5)
C4-C5	1.534 (6)	C4-C8	1.536 (6)
C4-C9	1.528 (6)	C5-C6	1.531 (5)
C6-C7	1.527 (6)	C9-C10	1.398 (6)
C9-C14	1.392 (6)	C10-C11	1.394 (6)
C11-C12	1.366 (6)	C11-O2	1.376 (5)
C12-C13	1.378 (6)	C13-C14	1.388 (6)
C15-O2	1.415 (6)		

Intermolecular Distances (Å)

N1····O1	2.789
N1····N1	3.009
O1····O1	3.257

Bond Angles (°)

O1-N1-C1	113.4 (4)	C11-O2-C15	119.0 (4)
N1-C1-C2	126.8 (4)	N1-C1-C6	117.3 (4)
C1-C2-C3	110.3 (4)	C1-C2-C6	115.8 (4)
C2-C3-C4	113.9 (3)	C3-C4-C5	106.6 (3)
C3-C4-C8	108.7 (4)	C3-C4-C9	110.3 (3)
C5-C4-C8	109.7 (3)	C5-C4-C9	108.8 (4)
C8-C4-C9	110.8 (3)	C4-C5-C6	115.2 (3)
C1-C6-C5	109.0 (3)	C1-C6-C7	114.4 (4)
C5-C6-C7	110.7 (4)	C4-C9-C10	121.5 (4)

C4-C9-C14	- -	120.9 (4)	C9-C10-C11	- -	120.5 (4)
C9-C10-C14	- -	117.6 (4)	O2-C11-C10	- -	123.6 (4)
O2-C11-C12	- -	115.2 (4)	C10-C11-C12	- -	121.2 (4)
C11-C12-C13	- -	118.8 (4)	C12-C13-C14	- -	120.9 (5)
C9-C14-C13	- -	120.9 (4)			

Fractional Atomic Coordinates (Å)

Atom	x	y	z
O1	0.1979(6)	0.1298(3)	0.5146(3)
O2	1.2317(6)	0.4339(4)	1.3776(3)
N1	0.2326(6)	0.0468(3)	0.5833(3)
C1	0.4284(8)	0.0867(4)	0.6559(4)
C2	0.6129(8)	0.2101(4)	0.6777(4)
C3	0.7069(8)	0.3079(4)	0.8260(4)
C4	0.7744(7)	0.2327(4)	0.9102(4)
C5	0.5789(7)	0.1069(4)	0.8793(4)
C6	0.4815(8)	0.0048(4)	0.7317(4)
C7	0.2875(8)	-0.1151(4)	0.7128(5)
C8	0.9702(8)	0.1806(5)	0.8719(4)
C9	0.8339(7)	0.3330(4)	1.0583(4)
C10	1.0120(7)	0.3359(4)	1.1484(4)
C11	1.0599(8)	0.4259(4)	1.2835(4)
C12	0.9369(8)	0.5144(5)	1.3313(5)
C13	0.7601(9)	0.5118(5)	1.2437(5)
C14	0.7077(8)	0.4219(4)	1.1090(4)
C15	1.3404(9)	0.3284(6)	1.4526(5)

Table 4

X-Ray Crystallographic Data of (2*R*,1'*S*)-(+)-1-(1,2-Dihydro-7-methoxy-1,4-dimethyl-1-naphthyl)-N-methyltrifluoroacetyl-2-propylamine (120)

Bond Lengths (Å)

F1-C16	1.268(20)	F2-C16	1.331(18)
F3-C16	1.337(20)	N1-C13	1.498(16)
N1-C14	1.496(18)	N1-C15	1.340(18)
O1-C8	1.394(17)	O1-C19	1.415(17)
O2-C15	1.200(17)	C1-C2	1.566(17)
C1-C10	1.547(18)	C1-C11	1.572(18)
C1-C12	1.505(21)	C2-C3	1.540(20)
C3-C4	1.335(19)	C4-C5	1.464(18)
C4-C18	1.528(18)	C5-C6	1.363(18)
C5-C10	1.471(17)	C6-C7	1.406(19)
C7-C8	1.394(19)	C8-C9	1.375(20)
C9-C10	1.367(18)	C12-C13	1.532(18)
C13-C17	1.537(21)	C15-C16	1.606(20)

Bond Angles (°)

C14-N1-C13	119(1)	C15-N1-C13	115(1)
C15-N1-C14	125(1)	C19-O1-C8	118(1)
C10-C1-C2	108(1)	C11-C1-C2	106(1)
C11-C1-C10	109(1)	C12-C1-C2	109(1)
C12-C1-C10	115(1)	C12-C1-C11	110(1)
C3-C2-C1	109(1)	C4-C3-C2	121(1)
C5-C4-C3	121(1)	C18-C4-C3	122(1)
C18-C4-C5	116(1)	C6-C5-C4	124(1)
C10-C5-C4	119(1)	C10-C5-C6	117(1)
C7-C6-C5	123(1)	C8-C7-C6	118(1)

C7-C8-O1	- 123(1)	C9-C8-O1	- 116(1)
C9-C8-C7	- 121(1)	C10-C9-C8	- 121(1)
C5-C10-C1	- 117(1)	C9-C10-C1	- 123(1)
C9-C10-C5	- 120(1)	C13-C12-C1	- 115(1)
C12-C13-N1	- 112(1)	C17-C13-N1	- 107(1)
C17-C13-C12	- 119(1)	O2-C15-N1	- 127(1)
C16-C15-N1	- 116(1)	C16-C15-O2	- 117(1)
F2-C16-F1	- 109(1)	F3-C16-F1	- 109(1)
F3-C16-F2	- 106(2)	C15-C16-F1	- 112(1)
C15-C16-F2	- 113(1)	C15-C16-F3	- 107(1)

Fractional Atomic Coordinates (Å)

Atom	x	y	z
F1	0.36074(13)	-0.24521(7)	-0.58631(6)
F2	0.18819(15)	-0.17923(7)	-0.66126(6)
F3	0.13626(16)	-0.28228(9)	-0.55861(6)
O2	0.18229(16)	-0.43888(8)	-0.65511(6)
N1	0.3047(14)	-0.3490(8)	-0.7589(6)
O1	-0.2248(14)	-0.3831(7)	-0.6945(6)
C1	0.1213(18)	-0.4126(10)	-0.9378(8)
C2	0.1123(19)	-0.3650(10)	-1.0304(8)
C3	0.1524(20)	-0.2504(12)	-1.0256(9)
C4	0.1096(18)	-0.1929(10)	-0.9589(8)
C5	0.0262(17)	-0.2368(10)	-0.8867(8)
C6	-0.0501(19)	-0.1800(10)	-0.8277(8)
C7	-0.1371(19)	-0.2244(11)	-0.7623(8)
C8	-0.1396(20)	-0.3310(10)	-0.7555(9)
C9	-0.0620(19)	-0.3914(10)	-0.8125(8)
C10	0.0193(16)	-0.3490(9)	-0.8779(8)

C11	0.0564(19)	-0.5240(9)	-0.9462(9)
C12	0.2817(18)	-0.4171(10)	-0.9103(8)
C13	0.3075(19)	-0.4426(10)	-0.8150(9)
C14	0.3921(20)	-0.2566(11)	-0.7854(9)
C15	0.2406(20)	-0.3624(11)	-0.6818(9)
C16	0.2355(23)	-0.2630(13)	-0.6207(11)
C17	0.4585(20)	-0.4951(11)	-0.8004(10)
C18	0.1388(21)	-0.0776(10)	-0.9545(9)
C19	-0.2753(22)	-0.3276(12)	-0.6218(10)

Table 5

Least Squares Calculation of the Angle and Distance Between the Aromatic Ring the Trifluoroacetamide (120) Carbonyl Group

Input Data

a = 8.9918

b = 13.0422

c = 15.5108

α = 90.0000°

β = 90.0000°

γ = 90.0000°

Cartesian Coordinates in Angstroms

Atom	x	y	z	Plane
C5	0.248	-3.087	-13.758	1
C6	-0.439	-2.346	-12.836	1
C7	-1.248	-2.931	-11.819	1
C8	-1.243	-4.317	-11.718	1
C9	-0.582	-5.112	-12.606	1

C10	0.181	-4.554	-13.618	1
N1	2.750	-4.553	-11.772	2
O2	1.630	-5.725	-10.158	2
C14	3.517	-3.348	-12.183	2
C15	2.169	-4.727	-10.576	2

The Equation of Least Squares (LS) Plane 1

-0.796601x + -0.017599y + -0.604249z = 8.164528

The Error is 0.001203

Deviations From Plane 1 for the Points in Plane 1 (Å)

C5 Distance to LS Plane 1 is -0.006

C6 Distance to LS Plane 1 is -0.017

C7 Distance to LS Plane 1 is -0.023

C8 Distance to LS Plane 1 is 0.018

C9 Distance to LS Plane 1 is -0.006

C10 Distance to LS Plane 1 is -0.000

The Equation of Least Squares (LS) Plane 2

-0.854742x + 0.382833y + -0.350506z = 0.008334

The Error is 0.003553

Deviations From Plane 2 for the Points in Plane 2 (Å)

N1 Distance to LS Plane 2 is -0.024

O2 Distance to LS Plane 2 is 0.032

C14 Distance to LS Plane 2 is 0.026

C15 Distance to LS Plane 2 is -0.035

The Angle Between the Two Least Squares Planes is 27.63°

Distances From Plane 1 (Å)

F1 Distance to LS Plane 1 is 5.192

F2 Distance to LS Plane 1 is 3.285

F3 Distance to LS Plane 1 is 3.830

N1 Distance to LS Plane 1 is 3.167

O2 Distance to LS Plane 1 is 3.222

C13 Distance to LS Plane 1 is 2.645

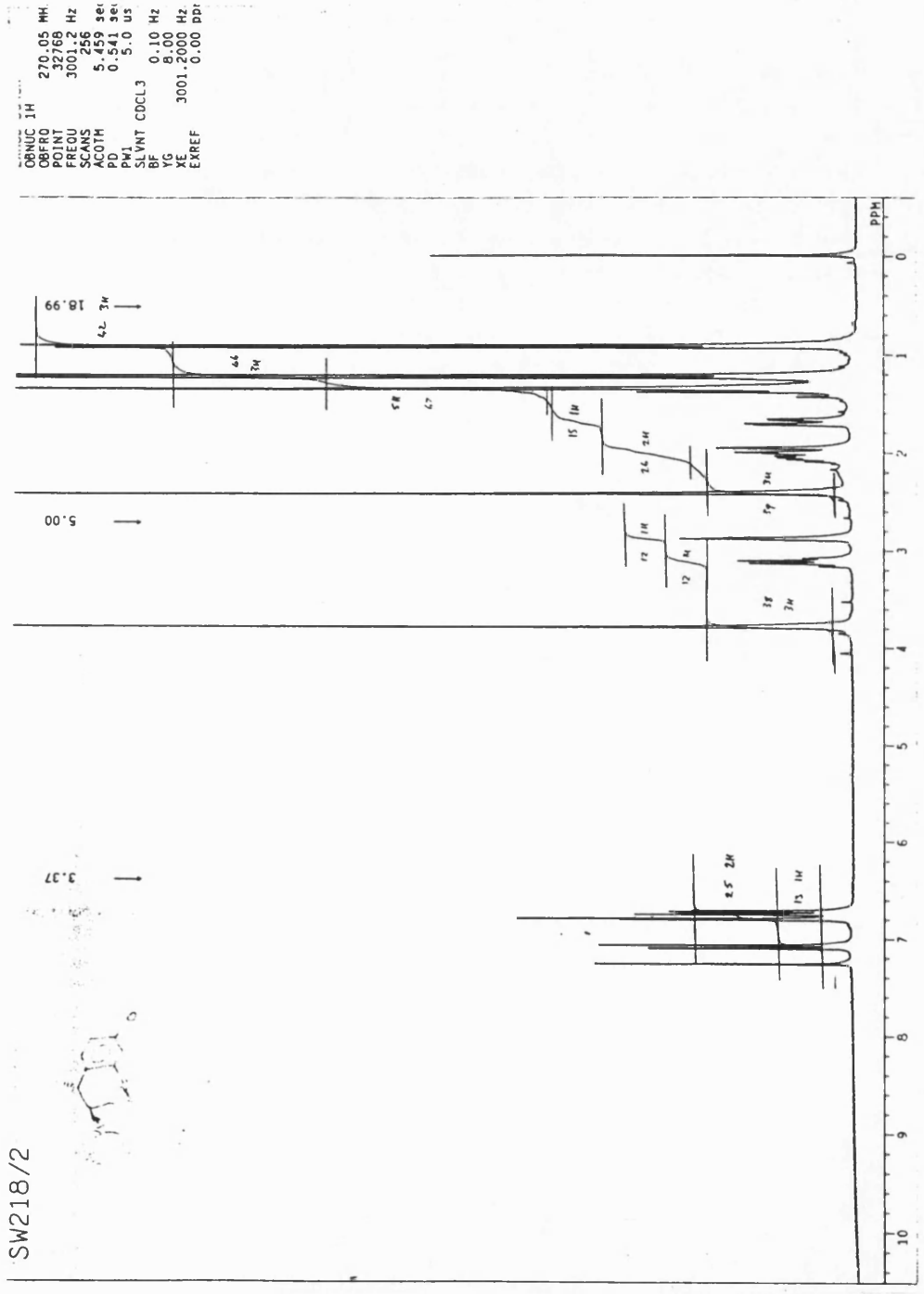
C14 Distance to LS Plane 1 is 3.553

C15 Distance to LS Plane 1 is 3.418

C16 Distance to LS Plane 1 is 3.982

APPENDIX B-

SPECTRA



^{1}H n.m.r. of (–)-(1*R*,2*S*,4*R*,6*R*)-1,2,3,4,5,6-Hexahydro-8-methoxy--1,3,4,6-tetramethyl-2,6-methano-3-benzazocine

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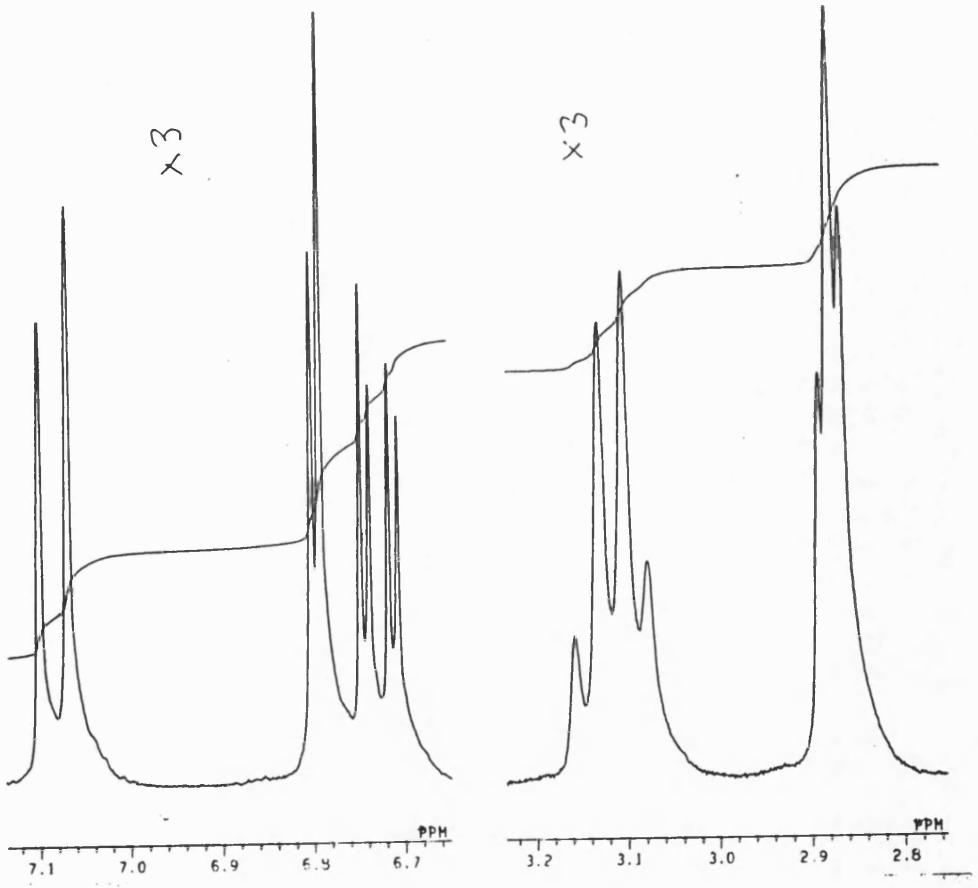

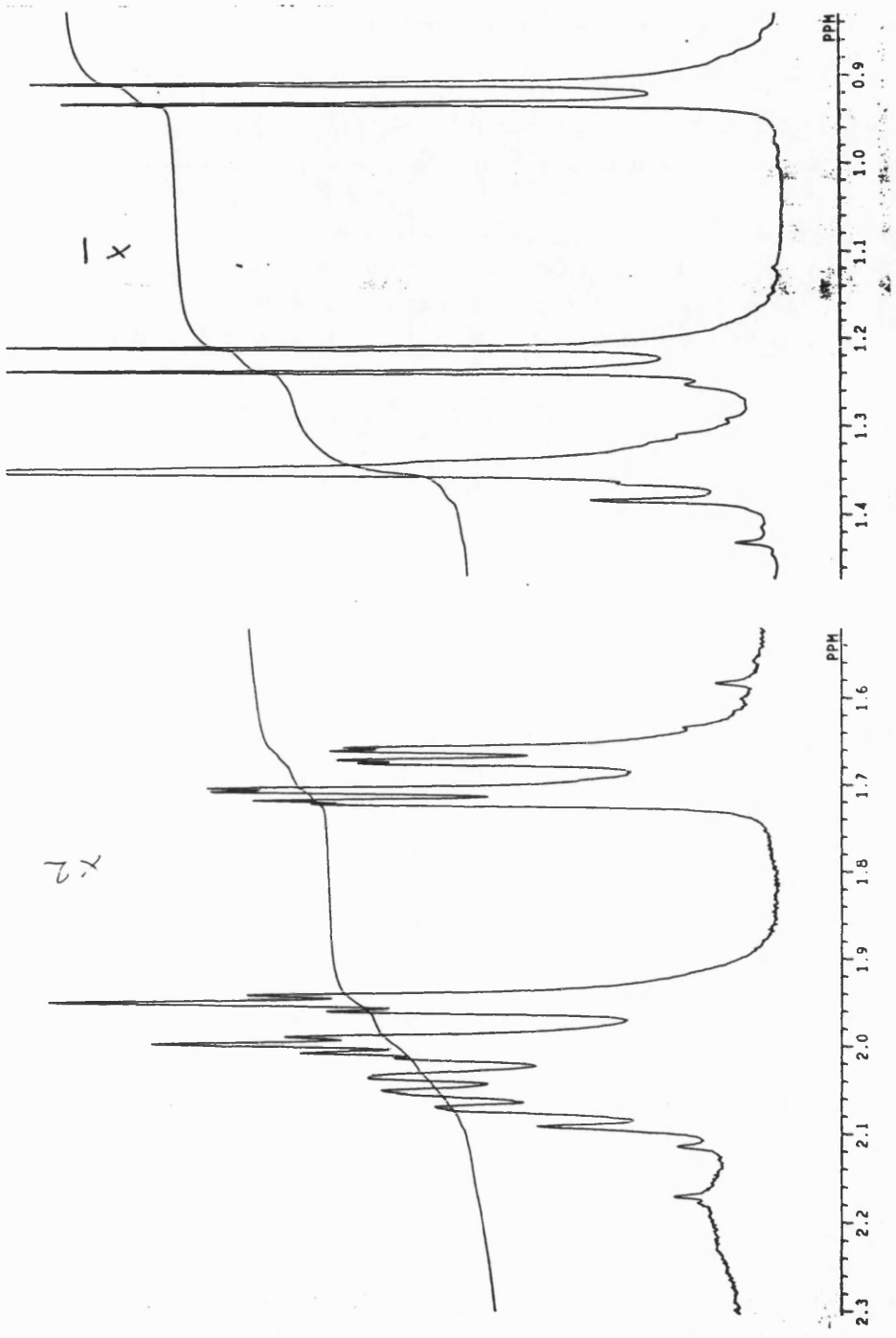
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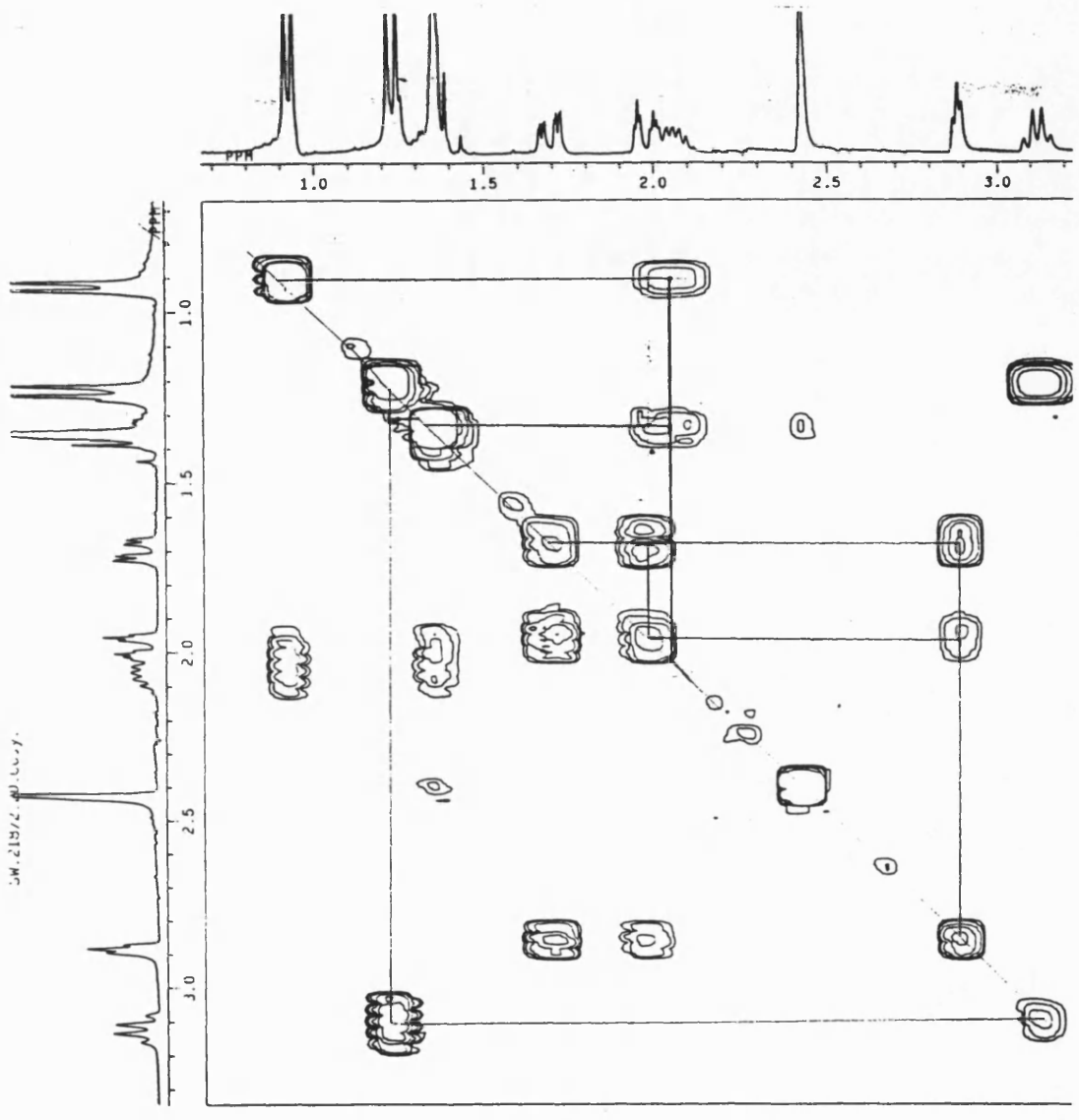
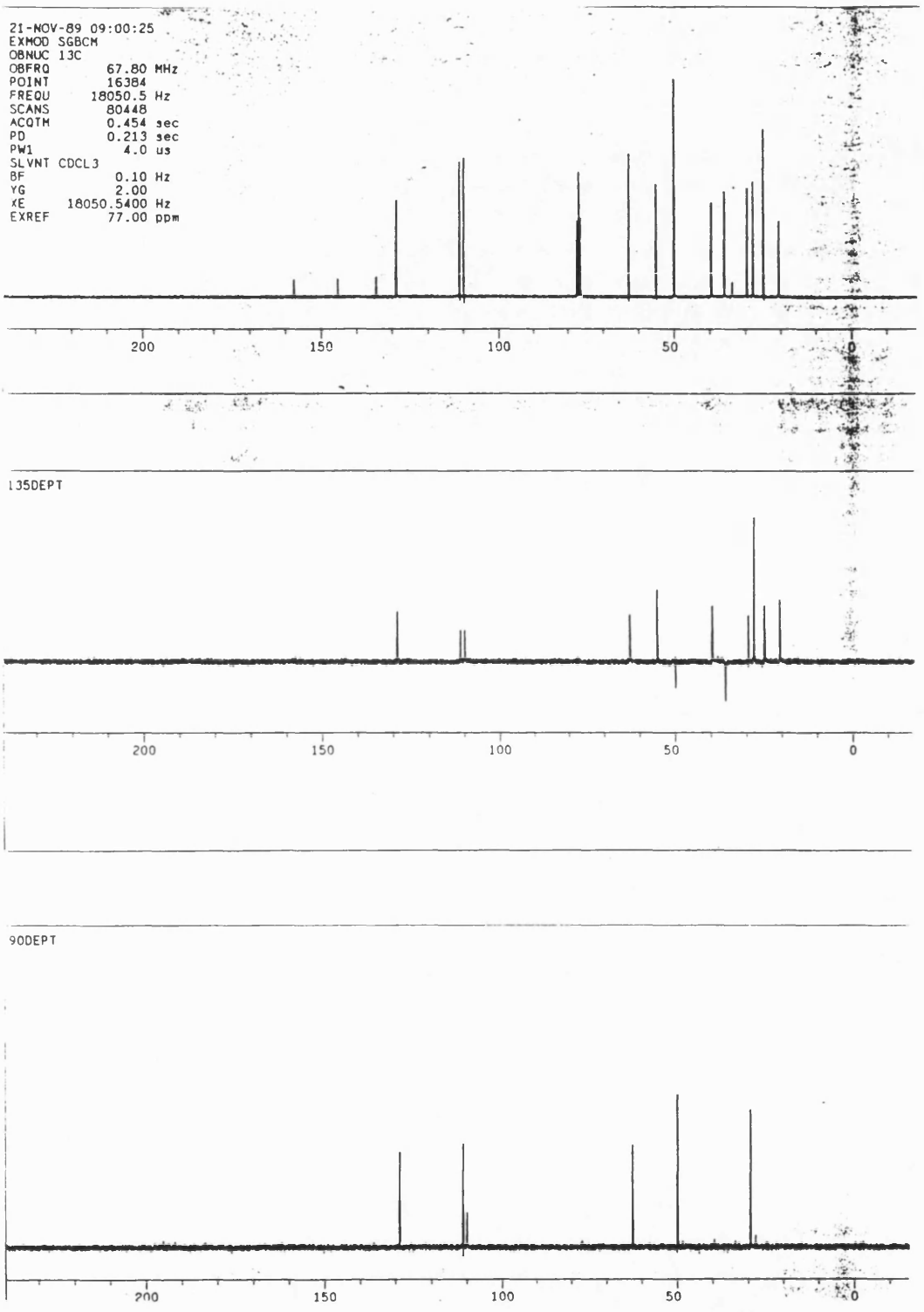
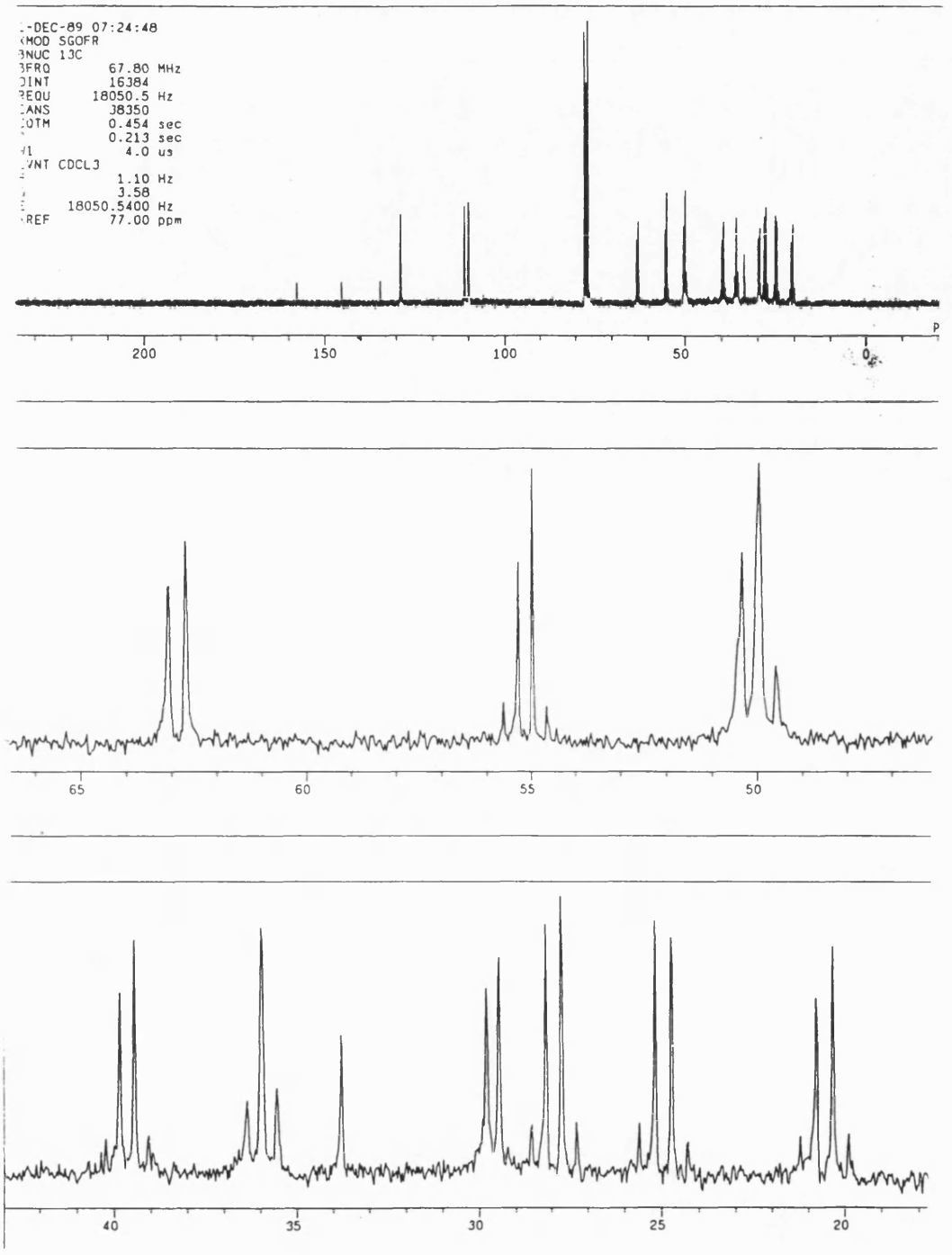


2D-COSY of (-)-(1*R*,2*S*,4*R*,6*R*)-1,2,3,4,5,6-Hexahydro-8-methoxy-1,3,4,6-tetramethyl-2,6-methano-3-benzazocine



^{13}C n.m.r. of (-)-(1*R*,2*S*,4*R*,6*R*)-1,2,3,4,5,6-Hexahydro-8-methoxy--1,3,4,6-tetramethyl-2,6-methano-3-benzazocine

SW.218/2.OFR.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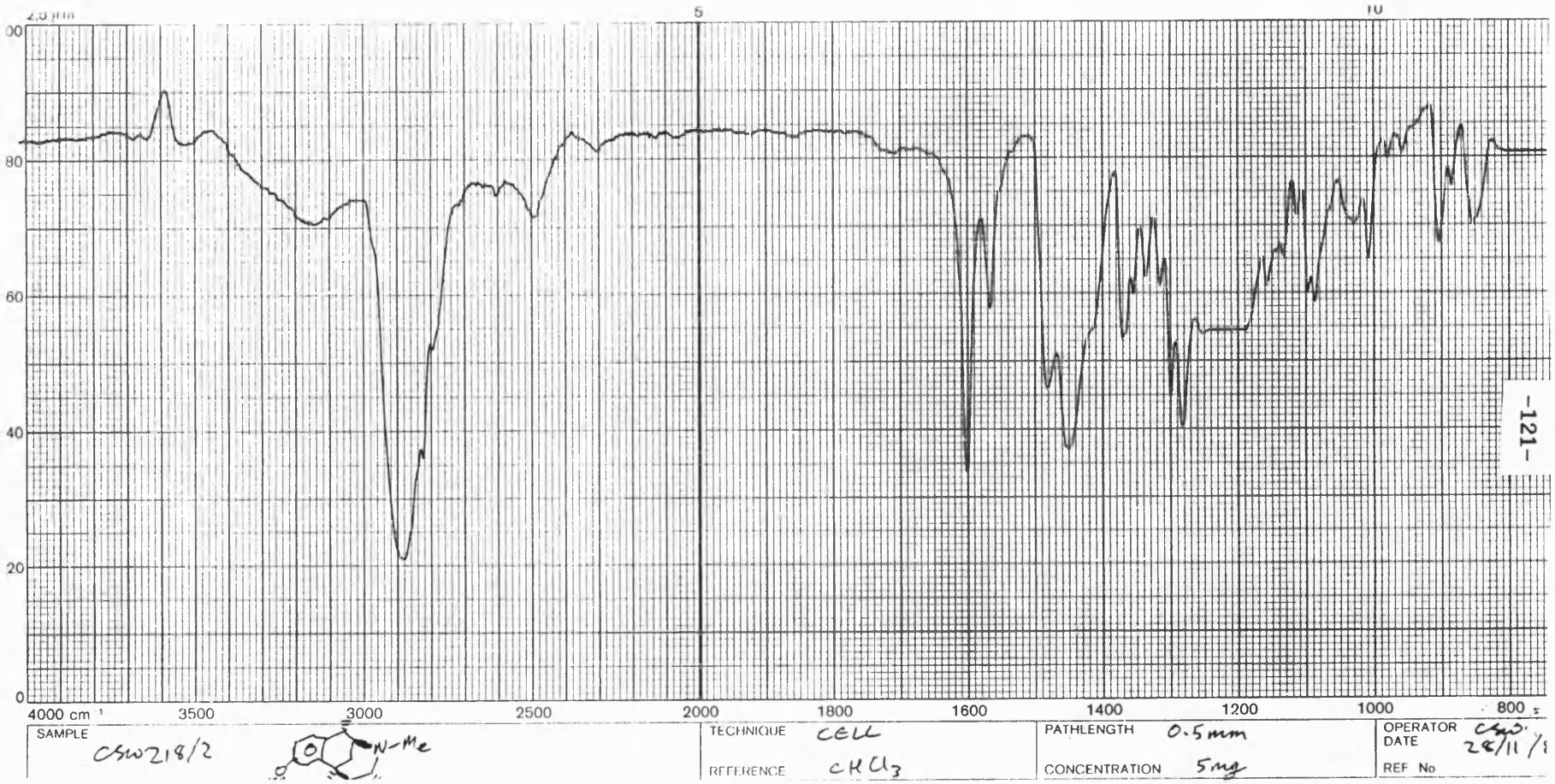

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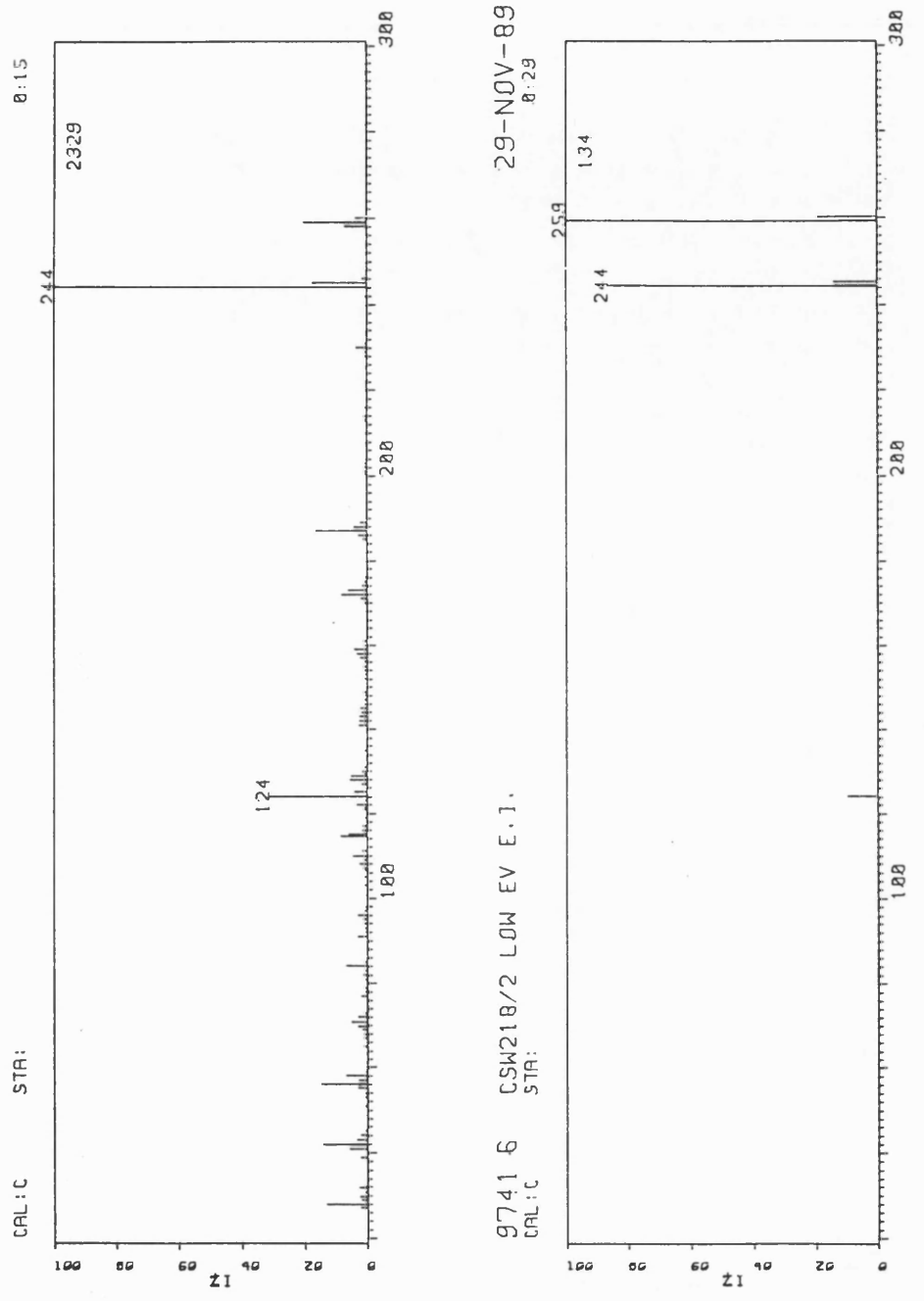
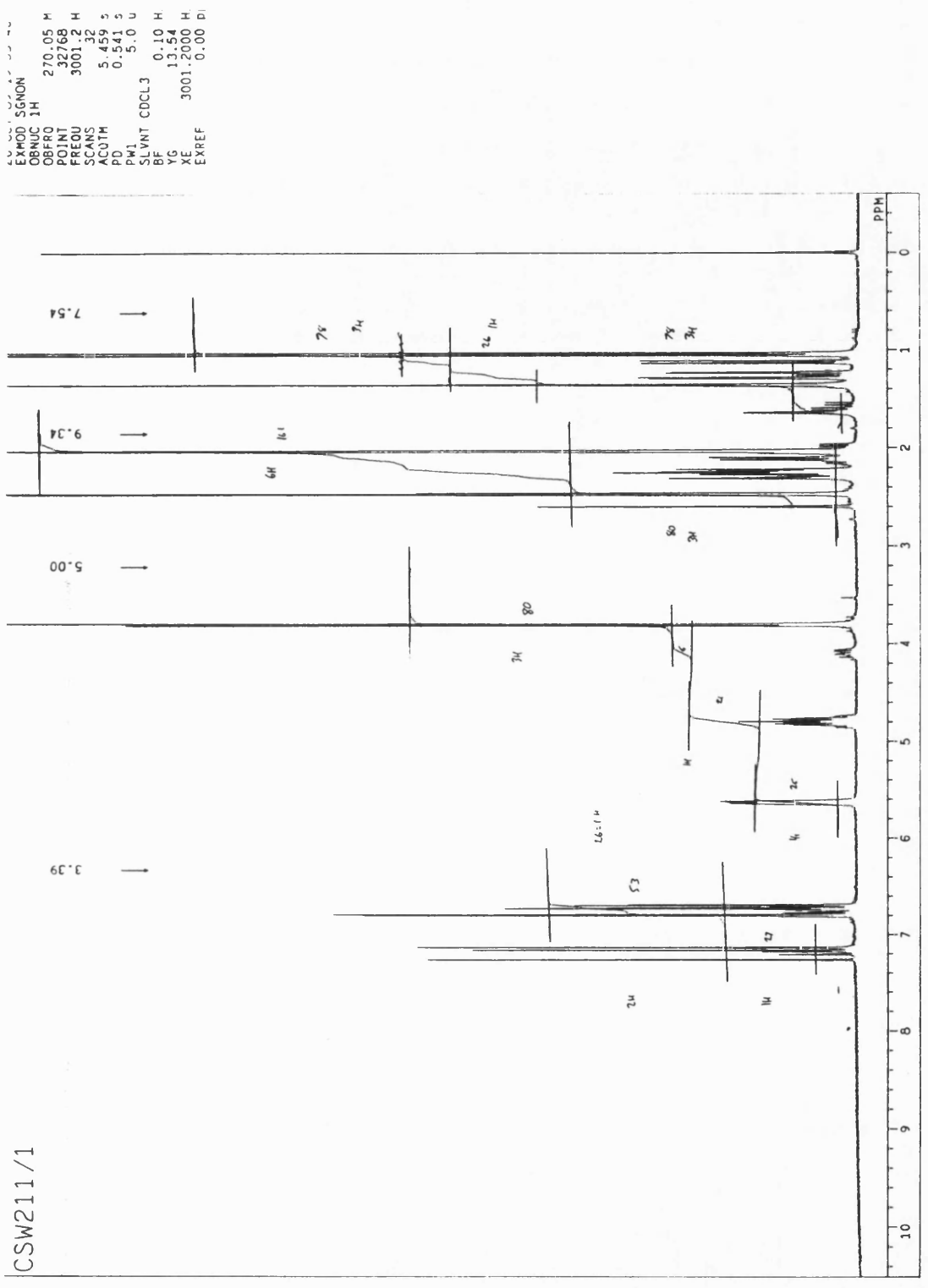
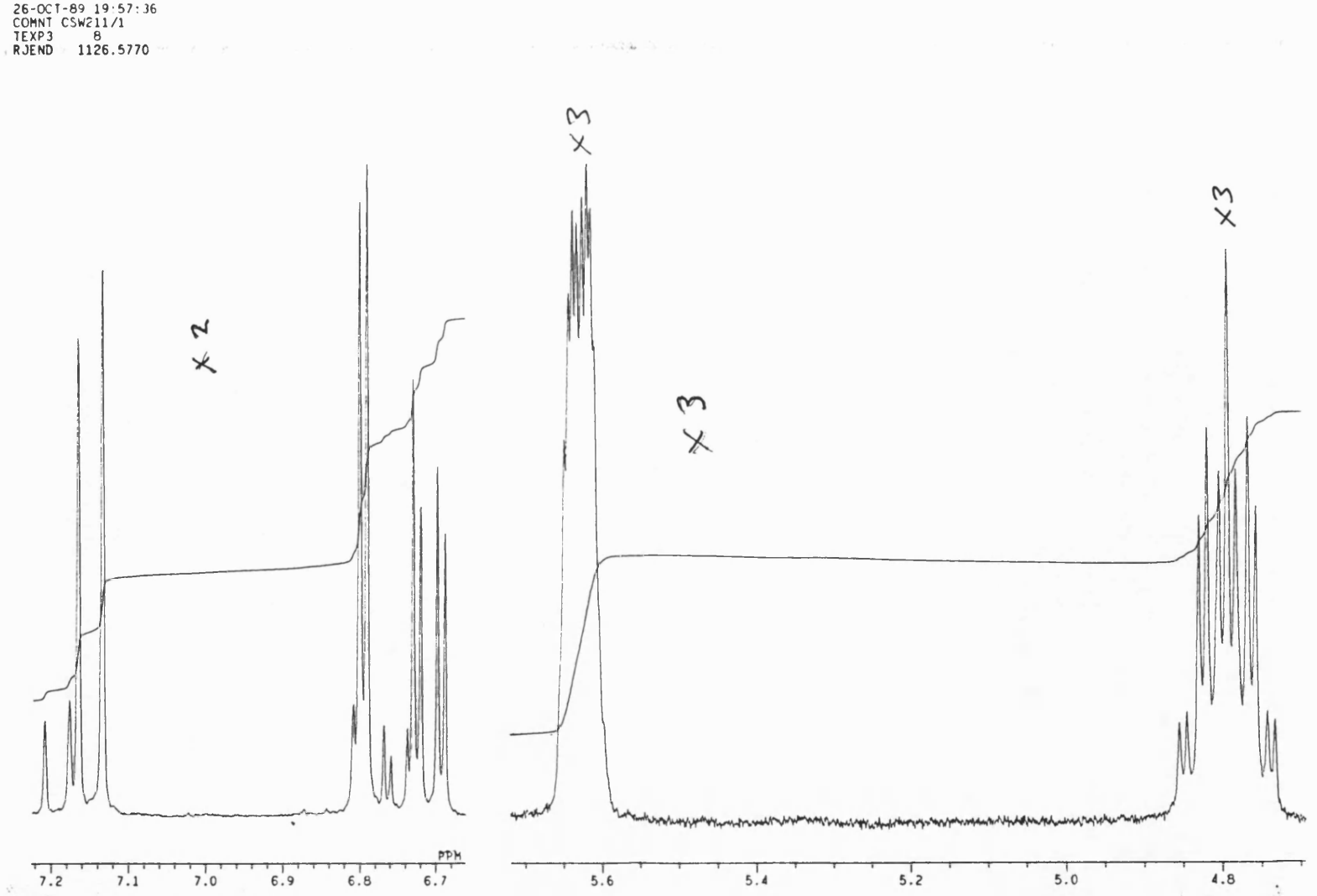


M.S. of (-)-(1*R*,2*S*,4*R*,6*R*)-1,2,3,4,5,6-Hexahydro-8-methoxy-1,3,4,6-tetramethyl-2,6-methano-3-benzazocine



^{1}H n.m.r. of (+)-(2*R*,1'*S*)-1-(1,2-dihydro-7-methoxy-1,4-dimethyl-1-naphthyl)-*N*-methyltrifluoroacetyl-2-propylamine (120)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x3
x3
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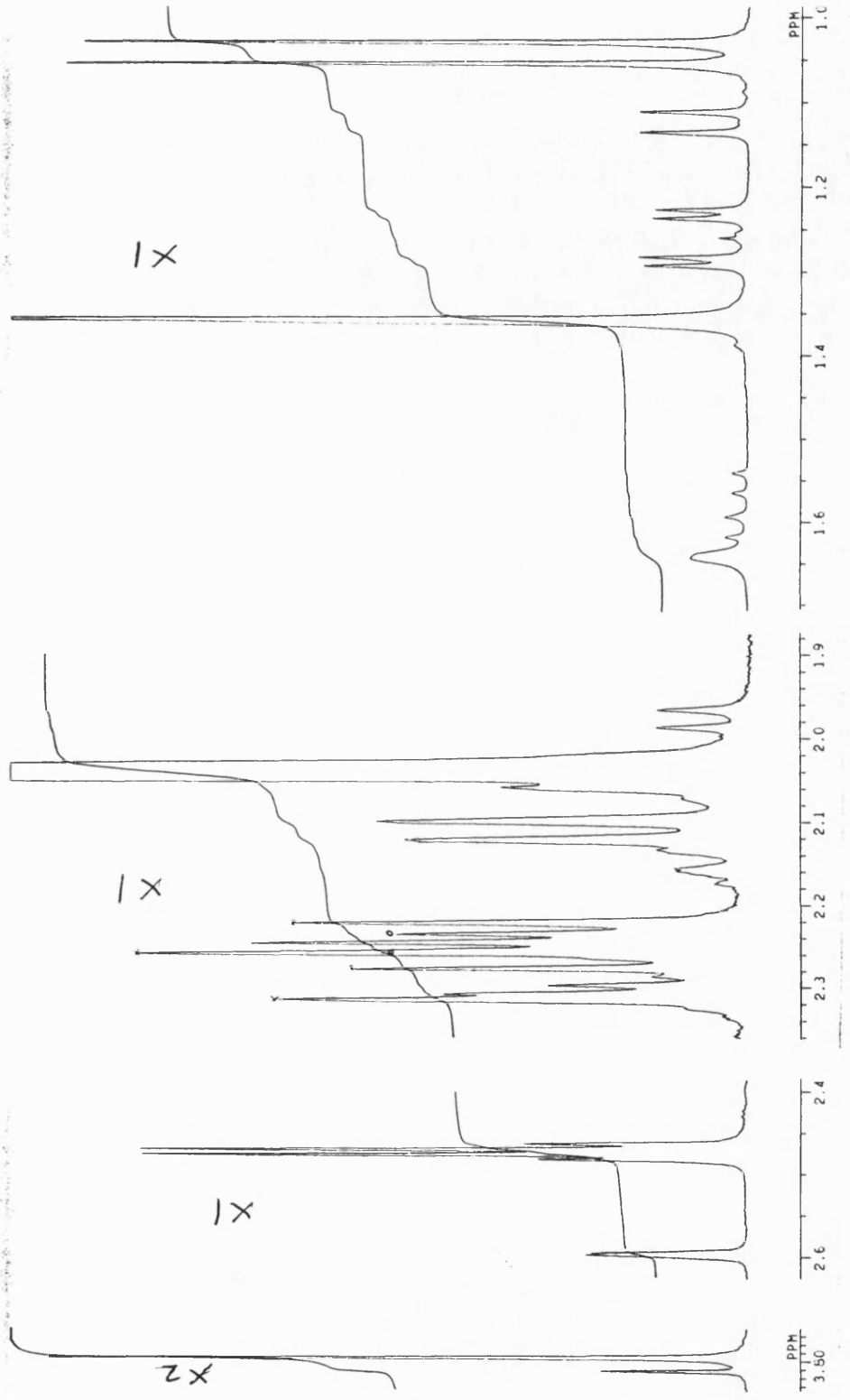
7.0
6.9
6.8
6.7
5.6
5.4
5.2
5.0
4.8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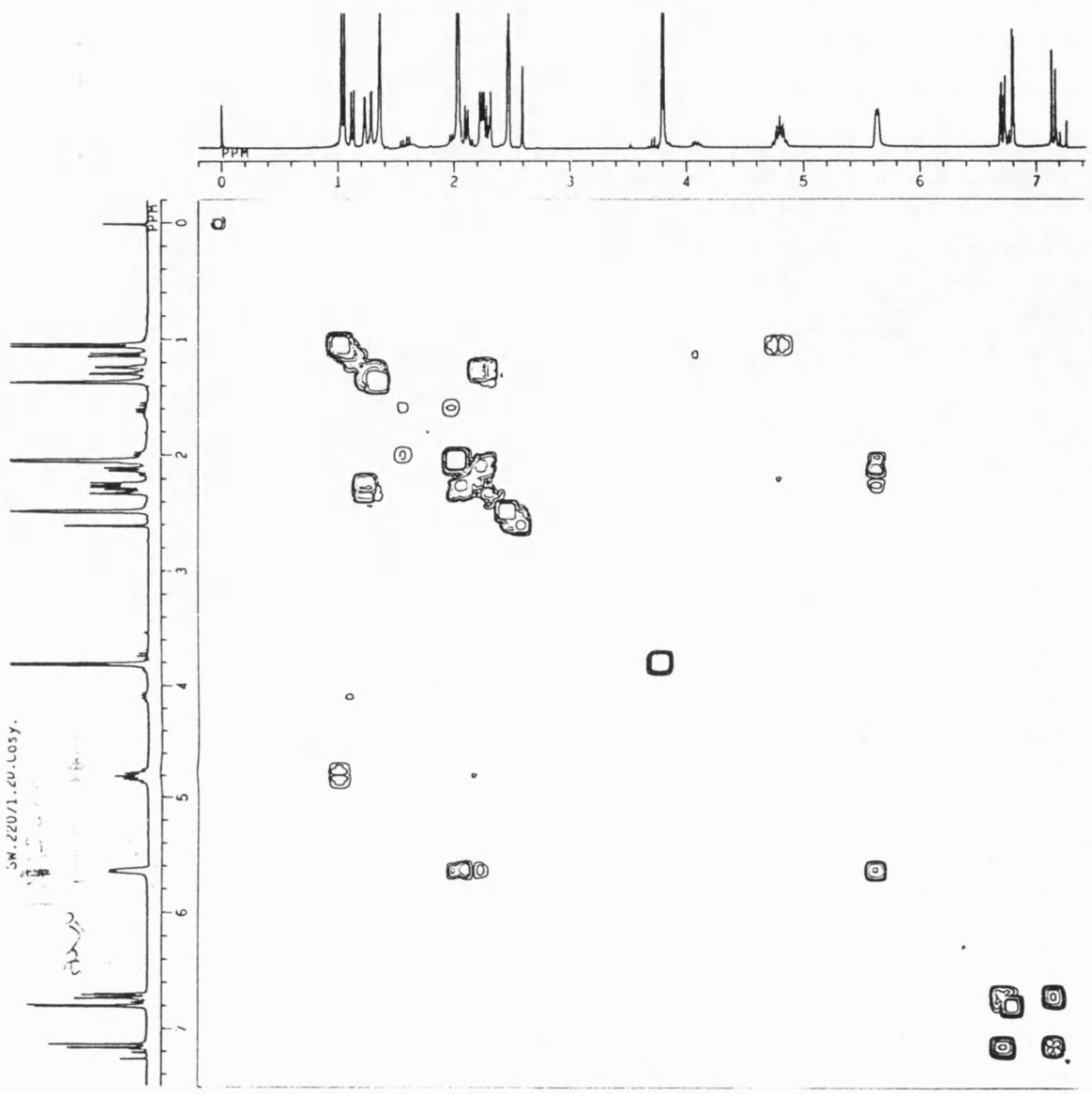
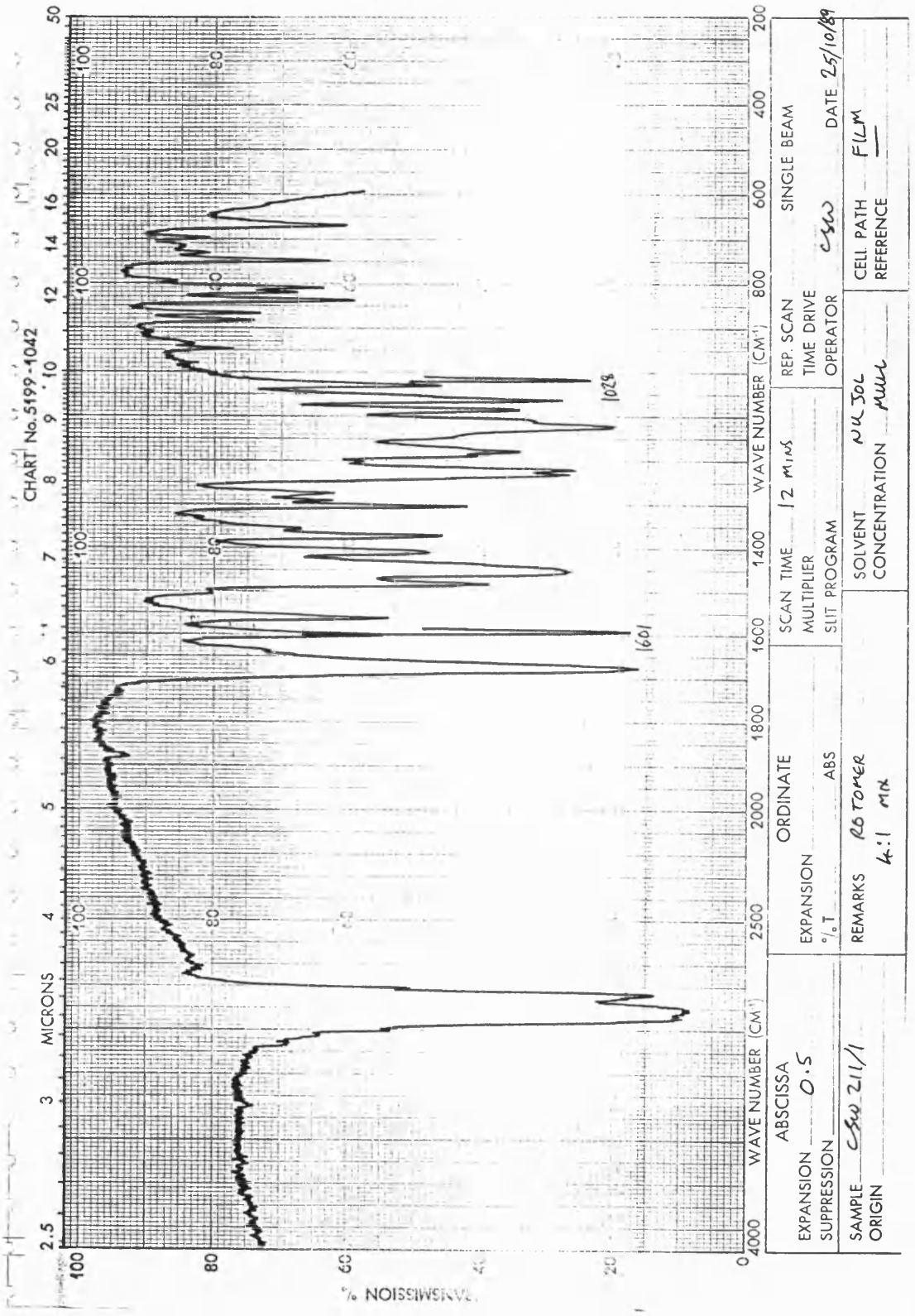
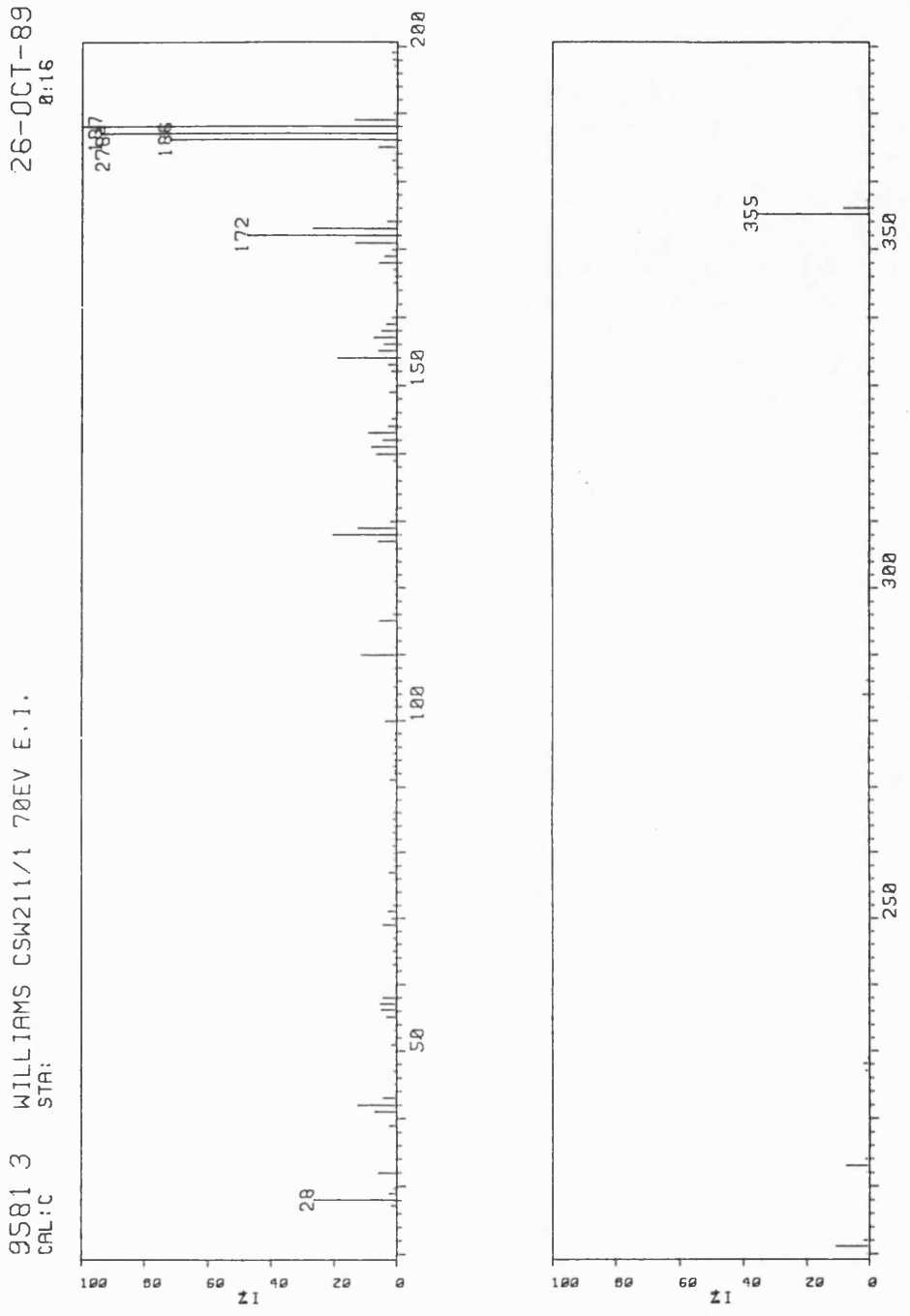
PPM



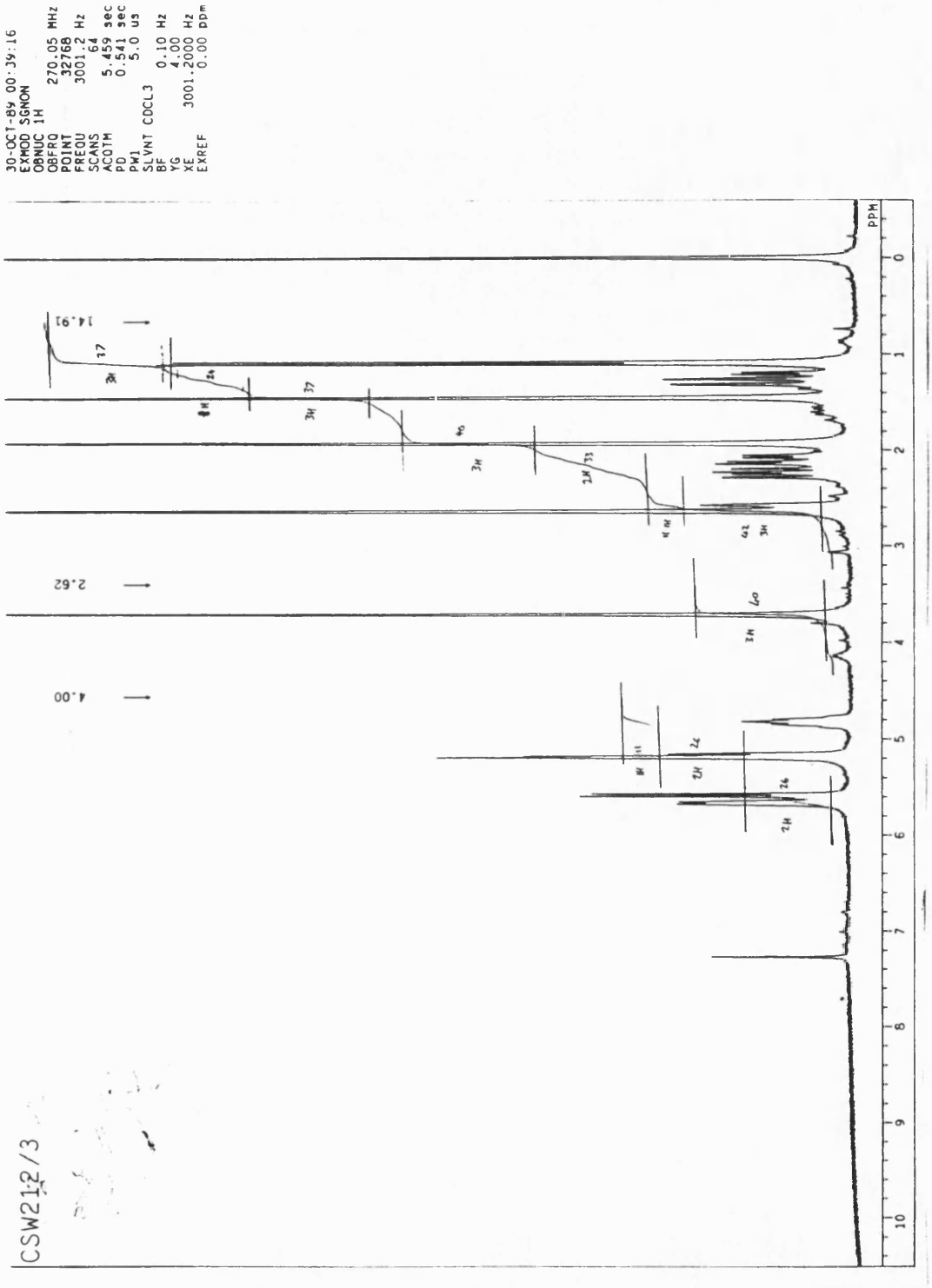
2D-COSY of (+)-(2*R*,1'*S*)-1-(1,2-dihydro-7-methoxy-1,4-dimethyl-1-naphthyl)-*N*-methyltrifluoroacetyl-2-propylamine



I.R. of (+)-(2*R*,1'*S*)-1-(1,2-dihydro-7-methoxy-1,4-dimethyl-1-naphthyl)-*N*-methyltrifluoroacetyl-2-propylamine



M.S. of (+)-(2*R*,1'*S*)-1-(1,2-dihydro-7-methoxy-1,4-dimethyl-1-naphthyl)-*N*-methyltrifluoroacetyl-2-propylamine



^{1}H n.m.r. of η^6-trans-[(2*R*,1'*S*)-1-(1,2-dihydro-7-methoxy-1,4-dimethyl-1-naphthyl)-*N*-methyltrifluoroacetyl-2-propylamine]chromium tricarbonyl

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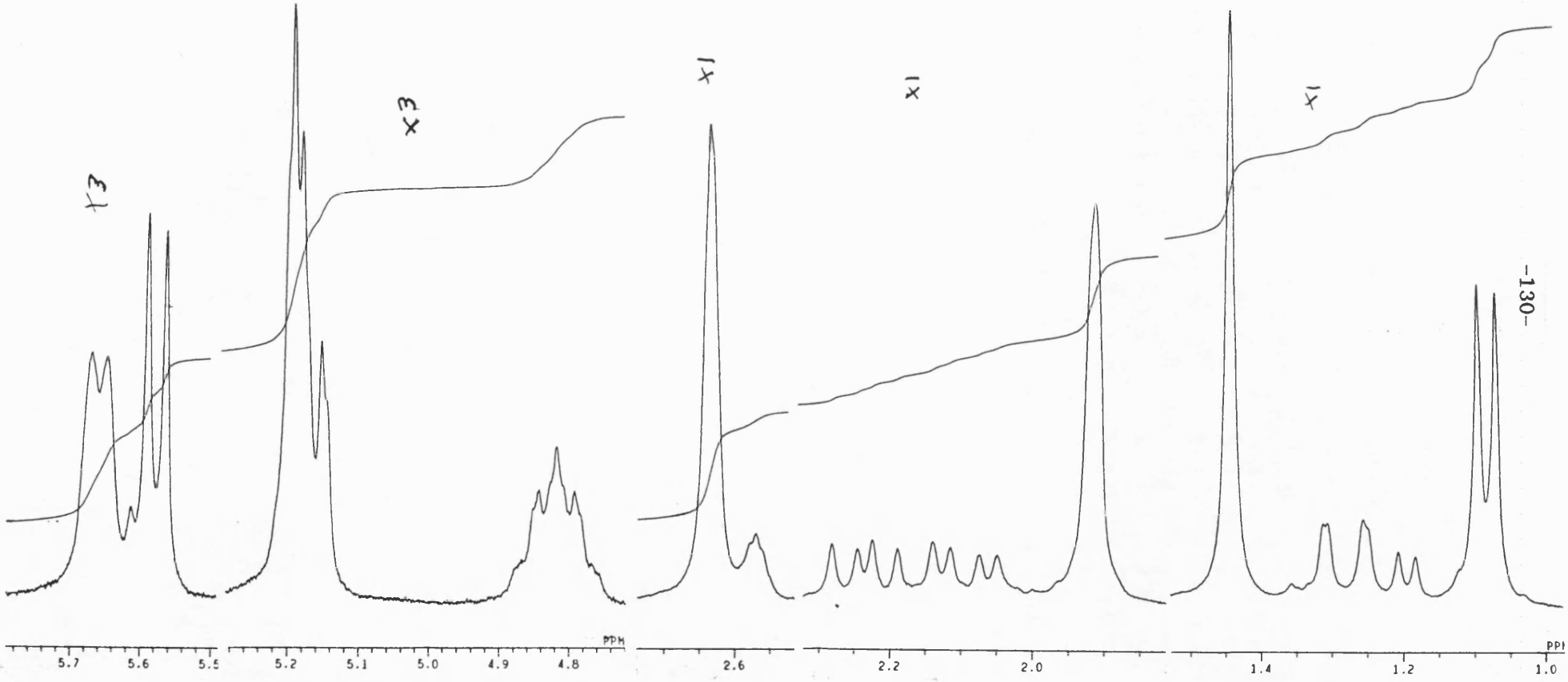
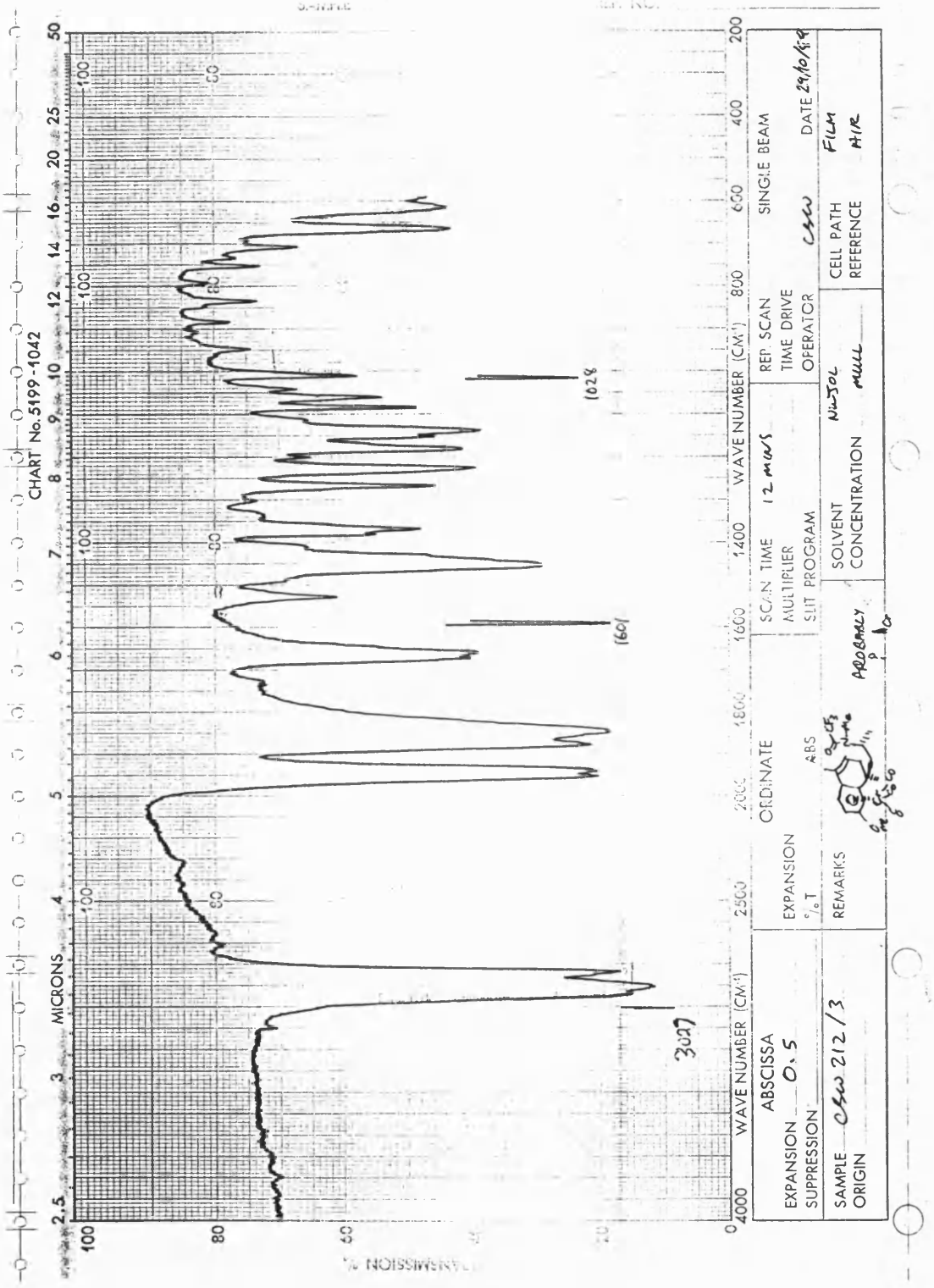
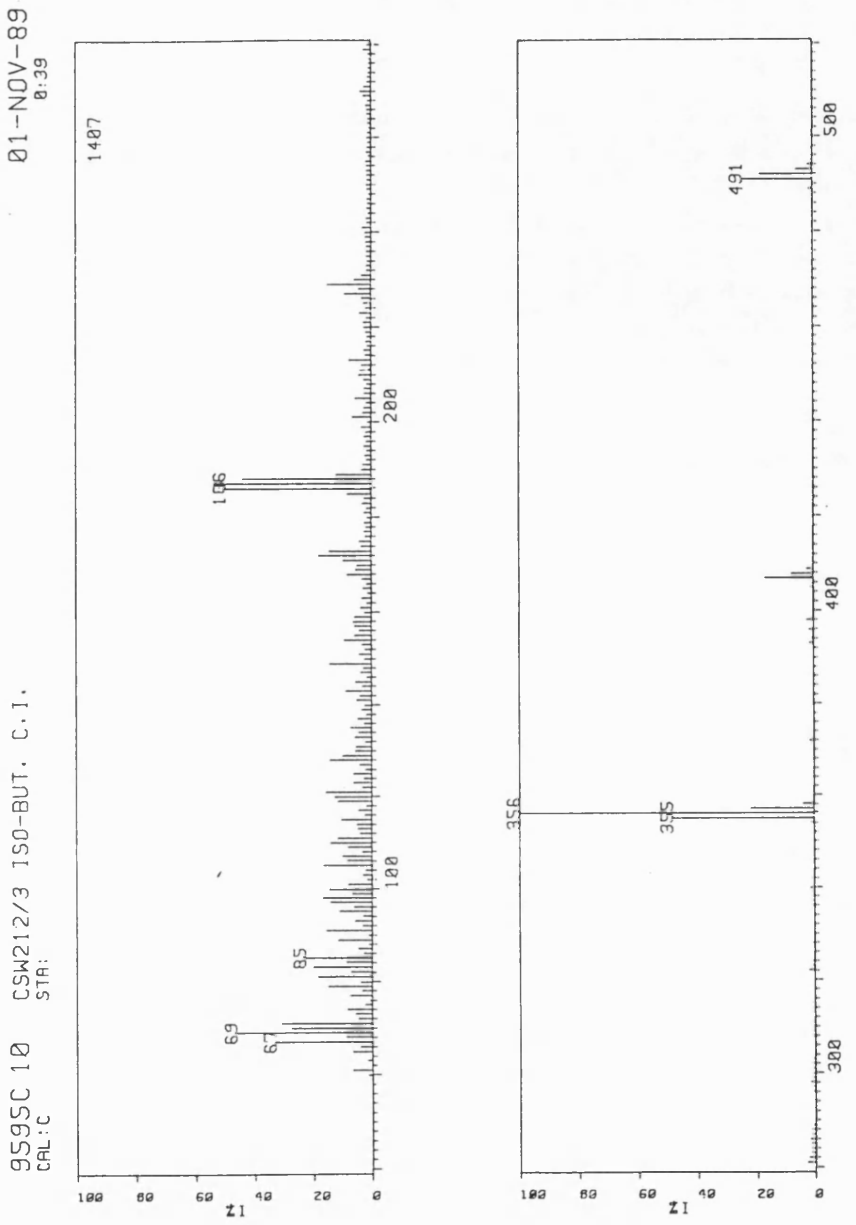




I.R. of η^6-trans-[(2*R*,1'*S*)-1-(1,2-dihydro-7-methoxy-1,4-dimethyl-1-naphthyl)-*N*-methyltrifluoroacetyl-2-propylamine]chromium tricarbonyl



M.S. of η^6-trans-[(2*R*,1'*S*)-1-(1,2-dihydro-7-methoxy-1,4-dimethyl-1-naphthyl)-*N*-methyltrifluoroacetyl-2-propylamine]chromium tricarbonyl